



# FEDERATION PROCEEDINGS

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## CANCELLATION OF THE 1945 FEDERATION ANNUAL MEETING

Which was scheduled to be held in Cleveland

May 8, 9, 10, 1945

Application, signed by the Federation Chairman and Secretary, was made to the War Committee on Conventions as created by the Director of War Mobilization and Reconstruction James F. Byrnes, with approval of the President, for permission to hold the 1945 Federation Annual Meeting, was made February 3, 1945. This permission was refused. On February 19, 1945 the Federation Secretary telegraphed the Secretaries of the Constituent Societies and the Chairman of the Cleveland Local Committee to this effect and on February 20, 1945 the Federation Secretary wrote the members of the Executive Committee in further explanation of the situation.

Thus the Federation Annual Meeting has been cancelled for the third consecutive year.

## THE AMERICAN PHYSIOLOGICAL SOCIETY

Abstracts of papers presented for the annual meeting scheduled for Cleveland, May 8, 9, 10, 1945. On account of the cancellation of this meeting, all the papers are to be regarded as "read by title." For possible correction in any of the abstracts see the next issue.

**Section of the corpus callosum in the monkey.**  
H. W. ADES (introduced by George Bachmann)  
*Emory University School of Medicine.* Effects of partial and complete section of the corpus callosum have been studied in five monkeys. The most characteristic result is an extreme hesitancy of reaction, amounting almost to complete blocking at times. When analyzed more closely, the main factor seems to be an inability rapidly to coordinate movements of the two sides, so that if the animal is compelled, for example, to make a response involving reaching with one hand, he tends to fall very slowly to the opposite side, occasionally completely losing his balance.

Callosal section in animals that have recovered from bilateral motor area removals produces a much more profound, but qualitatively similar result. In either case, compensation of effects of callosal section takes place very rapidly, so that within a week after operation it is difficult to detect any trace of the callosal syndrome.

**Dehydration produces intolerance to heat.**  
E. F. ADOLPH. *Dept. of Physiology, School of Medicine and Dentistry, Univ. of Rochester, Rochester, N. Y.* Mammals of 7 species were induced to lose water by vaporization during exposures to dry hot atmospheres such that the rectal temperature was ordinarily maintained below 40°C.

After water equal to about 10 per cent of the body weight had been lost, the deep temperature might climb explosively. If early withdrawn from the heat; animals suffered no after-effects and might dehydrate still further. If the rectal temperature exceeded a critical value, peculiar to each species

(41.7° to 43.5°), death promptly ensued. If withdrawn at the critical threshold, the animal might recover its water content and body temperature, but suddenly die without hyperthermia 2 to 26 hours later (dog, rabbit, guinea pig, rat). Desert death was observed also in cat and mouse.

Mouse and rat do not pant or sweat appreciably, and for 8 hours withstood only 38° dry-bulb. Guinea pig and rabbit withstood 43°. These four species drink little or no water when available during exposure to heat. Dog, cat and man tolerated dry atmospheres above 53° for 8 hours even without water; dog for at least 32 hours with water.

The explosive rise of deep temperature occurred at 10 to 17 per cent weight deficit in dog; occasionally at 5 to 10 per cent in man and other species. Further rapid dehydration could not be secured by exposure to heat.

Evidence indicated that the lethal intolerance to heat during dehydration was not due to failure of panting or evaporation or heart. But circulation of blood was impaired peripherally until transport of heat to sites of cooling became inadequate. [Work done under contract with the Office of Scientific Research and Development.]

The effects of blood flow and anoxia on the activity of spinal cardiovascular centers. ROBERT S. ALEXANDER (by invitation) and ROBERT F. PITTS. *Dept. of Physiology, Cornell Univ. Medical College, New York, N. Y.* The spinal cardiovascular centers in the upper thoracic cord of the cat were acutely isolated from all sources of afferent impulses by a low cervical section of the spinal

cord, a mid-thoracic section of the cord and sympathetic trunks, and section of all dorsal roots between levels of cord transection. In these acute deafferent spinal preparations, the presence of some residual tonic sympathetic activity arising within the spinal cardiovascular centers was demonstrated directly by recording the activity in the inferior cardiac nerve. This tonic activity becomes minimal under conditions of optimal lung ventilation and is greatly stimulated by asphyxiation. The asphyxial stimulation can not be reproduced by hypereapnia in the presence of adequate oxygen, but is caused by anoxia which produces a marked increase in the tonic sympathetic activity.

A rise in thoracic blood pressure produced by injections of adrenalin or pitressin or by sudden occlusion of the abdominal aorta depressed the tonic sympathetic activity in the deafferent spinal preparation. However, this inhibition could not be obtained unless there was adequate aeration of the blood in the lungs. This indicates that the rise in blood pressure inhibits activity by increasing blood flow and hence the oxygen supply to the spinal cardiovascular centers.

In the normal animal the buffer reflexes controlling cardiovascular sympathetic tone are undoubtedly dominant to any direct action of anoxia on spinal cardiovascular centers, but it is suggested that the local oxygen tension may play a subsidiary rôle in determining the general excitatory state of these centers.

**A study of some respiratory characteristics of intermittent pressure breathing.** SHANNON C. ALLEN (by invitation) and HOWARD G. SWANN. *Aero Medical Laboratory, Air Technical Service Command, Wright Field, Dayton, O.* Several characteristics of respiration at ground level and 45,000 feet were examined, employing an intermittent pressure breathing valve (Bennett type) imposing a high inspiratory and relatively low expiratory mask pressure with voluntary control of respiration.

Oxygen saturation (Milliken oximeter) at 45,000 feet averaged 90 per cent with the valve set to give a mask pressure of 8.6 inches ( $H_2O$ ) at the end of inspiration and 4.8 inches at the end of expiration. This value corresponds to one predicted at this altitude with 8 inches intra-pulmonary pressure only if alveolar  $pCO_2$  is reduced to 25.5 mm. Hg. Actually a  $pCO_2$  of 30 mm. was found in samples taken at the end of expiration.

Characteristics of respiratory pattern and mask pressure changes were measured with the optical flow-meter developed by the Physiological Branch, Aero Medical Laboratory. These were found to be similar at ground level and altitude but inspiratory minute volume (ambient) was approximately 5% per cent greater than normal resting ventilation without pressure.

Since it has been assumed that oxygen saturation is increased at extreme altitudes in direct relation to the added partial pressure of oxygen imposed by pressure breathing, the actual amount of pressure exerted during the respiratory cycle with continuous and intermittent pressure breathing were contrasted. Assuming a hypothetical condition in which the maximum observed mask pressure is imposed constantly throughout the cycle as an optimum pressure, continuous pressure breathing was found to exert 85 per cent of the hypothetical optimum pressure and intermittent pressure breathing only 65 per cent.

**Effect of auditory cortex lesions on correct conditioned auditory differential responses in dogs.** WILLIAM F. ALLEN. *Dept. of Anatomy, Univ. of Oregon Medical School, Portland.* Tunturi has described 3 different areas in the sylvian and ectosylvian gyri of dogs for localization of pitch. A dorsal one is here designated as A, a ventral one B and a ventro-cephalic one C. The problem is to determine the effects of destroying these areas on *correct conditioned differential responses* of the foreleg to two different sounds and to two different rates of the same sound.

**Results:** Deleting areas A, B, C, or B and C on both sides produced slight or no effect on either set of correct conditioned differential responses. Eliminating areas A and B, bilaterally, disrupts somewhere the usual mechanism for evoking correct conditioned differential responses for either set of analysers to the extent that from 370 to 484 tests were necessary before the first signs of differential responses appeared with the two different sounds. Similar sound mechanisms were ultimately reestablished, possibly in area C. They functioned accurately, but possessed other features which were decidedly inferior. Bilateral destruction of areas A, B and C prevented in most dogs the reappearance of correct conditioned differential responses with either set of analysers in over 1100 tests for each dog, suggesting inability to form a new sound association mechanism. The first and chief effect noted from the lesions is one involving *correct inhibition*, inability to hold back foreleg flexion during a negative conditioned test.

**The objective evaluation of therapy in hemorrhagic shock.<sup>1</sup>** J. B. ALLISON (by invitation), W. H. COLE (by invitation), W. W. WALCOTT (by invitation), S. GELFAN, W. S. ROOT and M. I. GREGERSEN. *Dept. of Physiology, College of Physicians and Surgeons, Columbia Univ.* The progressive changes which occur in unanesthetized dogs immediately after a single massive hemorrhage (Walcott, 1945) and the effect of replacement therapy were studied. The following determina-

<sup>1</sup> This work was done under a contract, recommended by the Committee on Medical Research, between the Office of Scientific Research and Development and Columbia University.

tions were made: blood volume, hematocrit, serum protein, arterial blood pH, blood pressure, heart rate, venous and arterial urine phosphate. The BHCO<sub>3</sub> level was perhaps the most reliable single criterion of the condition of the animal during shock and of the effectiveness of therapy.

When their blood pressure had fallen to 25 mm. Hg or less (terminal stage), 22 dogs were transfused with whole blood, 16 with plasma, and 4 with saline. In each instance the volume transfused was equal to the volume of blood removed. In these experiments saline produced no permanent recovery. The effectiveness of whole blood and plasma replacement varied with the condition of the animal at the time of transfusion.

Our experience with hemorrhage and transfusion indicates that the significance of survival percentage can be accurately evaluated only when the animal's condition is estimated by the simultaneous use of several of the criteria mentioned above. Indeed, it is possible by such means to follow the progressive development of shock and to measure the transitory or permanent recovery after transfusion.

The projection of the retina on the superior colliculus of the cat.<sup>1</sup> JULIA T. APTER (introduced by Samuel A. Talbot). *Wilmcr Ophthalmological Institute of the Johns Hopkins Hospital and University, Baltimore, Md.* The projection of the visual field or retina on the superior colliculus of 21 cats was investigated by means of an electrophysiological method whereby a 4.2° square of light was flashed for 10 msec. on a known position on the visual field while action potentials evoked by this stimulation of the retina were picked up from 40 points on the surface of each superior colliculus and recorded on a cathode ray oscillograph. The stimulus was moved and the potentials were again recorded. Each position of the spot stimulus in the visual field of one eye evokes a maximal potential (one with shorter latency and greater amplitude than any others) on a single, unique position on one colliculus. A chart relating each position of maximal potential on the superior colliculus to the location of the spot stimulus in the visual field producing that potential shows that the visual field is projected systematically on the surface of the superior colliculi.

Homonymous half-fields are projected on the contralateral superior colliculus, homonymous points in the fields being superimposed on the colliculus. The vertical meridian is found at the anterior margin of the colliculi and lateral field points at the posterior margin. The upper field is projected medial to the lower field. Points in the visual field near the horizontal and vertical meridians are projected to a wider area on the colliculus than are more peripheral points.

Rôle of the dorsal spinal roots in reflex vasodilatation. L. MATTHEW N. BACH (introduced by H. S. Mayerson). *Division of Physiology, Univ. of California Medical School, Berkley.* Previous evidence concerning the rôle of the dorsal spinal roots in reflex vasodilatation has been largely indirect since it was obtained from sympathectomized animals. In the (complementary) experiments to be reported here, rhizotomized animals were used.

Laminectomies were performed on cats, anesthetized with minimal doses of delvinal or nembutal, so as to expose the whole spinal cord, which was kept warm and moist at all times. All the dorsal roots (C4 to S3) were prepared so that simultaneous, immediate, and total rhizotomies could be performed. Similarly all the ventral roots from C8 to L1 were prepared so that an immediate and total separation of the peripheral portion of the sympathetic system from the central nervous system could be effected.

In five such preparations, the blood pressure, recorded from the femoral artery, ranged from 100 mm. to 150 mm. Hg. Depressor nerve stimulation (central end of the cut left vagus) evoked a decrease in blood pressure averaging 30 mm. Hg. Following total rhizotomies, the blood pressure rose to 180 mm. and stimulation of the depressor nerve failed to alter the blood pressure. Resection of the sympathetic outflow from the spinal cord caused a drop in blood pressure to around 100 mm. Hg. Stimulation of the depressor nerve again failed to cause any change in blood pressure.

These results provide presumptive evidence that fibers of the dorsal spinal roots may provide an important vasodilator motor pathway in the reflex arc of which the depressor nerve is the afferent limb.

Human centrifuge operation (motion picture).<sup>1</sup> E. J. BALDES and A. N. PORTER (by invitation). *Acceleration Laboratory, Mayo Aero Medical Unit, Rochester, Minn.* The motion picture illustrates the principles and the mechanism involved in the operation of the human centrifuge at the Acceleration Laboratory, Mayo Aero Medical Unit. The centrifuge has two essential parts: a superstructure or carriage and a pair of rotating flywheels. The superstructure and the flywheels rotate in the horizontal plane about a common axis. The flywheels are driven by a Chrysler automobile motor powered by natural gas. The rotating flywheels, which weigh approximately 20 tons apiece, provide the energy for the rapid development of accelerative forces in the superstructure. The superstructure is set in motion by clutching to the flywheels and is brought to a standstill by declutch-

<sup>1</sup> Work done under contracts with: (1) United States Army Air Forces, Wright Field, Dayton, Ohio, and (2) the Office of Scientific Research and Development, Research Council, Washington, D. C.

<sup>1</sup> This investigation was aided by a grant from the John and Mary Markle Foundation.

non-visual imagery and high alpha (hallucinations of schizophrenies were not so correlated.)

**Permanent motor disabilities induced by successive exposures to oxygen at high pressures.** (Moving picture.) JOHN W. BEAN and E. C. SIEGFRIED (by invitation). *Dept of Physiol., Univ. of Michigan, Ann Arbor.* Young adult albino rats were exposed to O<sub>2</sub> at 65 pounds pressure (gauge) for periods of from 10 to 25 minutes, depending on the animal's response, 2 to 4 times per day until a desired severity of chronic disability was induced. CO<sub>2</sub> was absorbed from the pressure chamber and in so far as possible the occurrence of convulsive seizures was avoided. Chamber temperature was maintained at about 24°C. Decompression was carried out over a period about equal to that of the animal's stay in the high pressure to avoid the possibility of bubble formation.

Individual reaction manifest following the animal's removal to room air after single exposures varied widely in type and severity; symptomatic recovery from these acute reactions usually occurred within a few minutes or hours. But with repeated exposures, commonly as few as 5 or 6 rarely after a single exposure, motor disabilities associated with spastic paralyses involving the limbs and body musculature and of a chronic nature were induced. Some symptomatic recovery from these chronic changes was evident but the persistence of striking disability for periods as long as 18 months when the animals were sacrificed indicate these changes are permanent.

Chicks (8 days old) exposed to O<sub>2</sub> at 90 and 65 pounds in a similar manner over a period of days were affected in a like manner so that the disabilities so induced persist into adult life. The nature of the disability point to possible permanent injury to the C.N.S. by the high O<sub>2</sub> pressure. Some of the reactions suggest visual disability.

**Influence of O<sub>2</sub> at high pressure on malarial parasites.** JOHN W. BEAN and RICHARD J. PORTER (by invitation). *Dept. of Physiology and The School of Public Health, Univ. of Michigan, Ann Arbor.* Pooled duckling or chick blood infected with plasmodium lophuriae was divided into test and control sample. The test samples were equilibrated with O<sub>2</sub> at high pressure. Test and control samples were then injected into normal chicks and parasite counts made 4 or 5 days later.

Exposure to O<sub>2</sub> at 90 pound (gauge) for 4 hours decreased the infectivity of the test blood to one-tenth that of the control blood. Test blood exposed to O<sub>2</sub> at 90 pounds for 6 hours failed to induce any detectable infection. Oxygen at 45 pounds for 6 and 12 hours markedly diminished but did not completely eliminate the infectivity of test blood; at 30 pounds for 3 hours it decreased the infectivity of chick test blood and after 12 hours exposure at

30 pounds this blood failed to induce any detectable infectivity of parasitized chick blood was also progressively decreased by 3, 6, 12 and 24 hour exposures at 15 pounds; the average parasite count following the 24 hour exposed test blood inoculation was 5 per 10,000 cells, that of the control was 2100 per 10,000. Parasites appeared more resistant in duck than in chick blood.

Attempts to lower the parasite counts of chick blood *in vivo* by successive exposure of infected chicks to O<sub>2</sub> at 90 pounds for short periods (about 4 mins.) were indecisive due to the high susceptibility of the birds to the toxic action of the O<sub>2</sub>.

**Changes in alveolar CO<sub>2</sub> tension resulting from compression.** JOHN W. BEAN. *Dept of Physiology, Univ. of Michigan, Ann Arbor.* Samples of air were taken at the end of expiration from the lungs of anesthetized dogs by an implanted catheter; the first was taken at atmospheric pressure. Compression (air) was then carried to slightly over 5.5 atms.; time for compression about 1.5 to 3.5 mins. The second sample was taken just after cessation of compression; the third a few minutes later. The pressure was then lowered to atmospheric and the fourth sample taken.

In 21 of the 22 compressions carried out on 4 animals the CO<sub>2</sub> tension in the lung just after cessation of compression was appreciably higher—from about 10 to 85 per cent—than that obtaining before compression was begun. Obviously the method does not provide an exact measure of the CO<sub>2</sub> in contact with the alveolar wall but it does provide a reasonably safe index of the direction of the CO<sub>2</sub> change in the alveoli.

This increased CO<sub>2</sub> tension may be best explained as due to the compressional inflow of air into the lung thus preventing exhalation of alveolar air during compression. Compressional inflow also tends to compress the alveolar air thus temporarily elevating the CO<sub>2</sub> tension in immediate contact with the wall.

It is concluded that the CO<sub>2</sub> thus dammed back in the blood and tissues constitutes a very important etiological factor in those reactions which occur in highly compressed air, especially in the early stages and which have been attributed by some authors solely to an hypothetical narcotic action of nitrogen.

**Effects of concussion upon the retention of learning in the guinea pig.** R. F. BECKER, R. A. GROAT (by invitation) and W. F. WINDLE. *Dept. of Anatomy and Inst. of Neurology, Northwestern Univ. Medical School, Chicago.* Guinea pigs weighing between 350 and 450 grams were trained to perfection on a simple, alternation-type maze. The criterion of learning was 10 perfect runs under 10 seconds each when 2 blind alleys alternated position in a chance sequence.

Six days after the initial learning a re-test for retention was run. All the animals exhibited perfect retention. A second investigator then selected certain animals at random from the trained pool and produced brain concussion in them. He was unaware of their performance on the maze. Controls were saved by random selection. Six days later the animals were given a second re-test by the first investigator. He did not know which had suffered concussion. The controls were effectively separated from the group because they showed perfect retention. Animals experiencing concussion took 12 trials on the average to reach the criterion of re-learning, made 9 errors on the average, and were prone to repeat errors in the same trial.

The brains of all animals which had been struck showed structural neuronal alterations, like those previously reported (*Surg. Gynec. and Obstet.* 79: 561, 1944). [Work done under contract, sponsored by CMR, between OSRD and Northwestern Univ.]

**Secretion and evaporation of sweat in cold weather.** H. S. BELDING (by invitation), G. E. FOLK (by invitation), W. H. FORBES and R. C. DARLING. *Fatiguc Laby., Harvard Univ., Boston, Mass.* Sweat secreted during bouts of exercise in the cold is only partially effective in achieving immediate skin cooling because a large proportion is recondensed in the clothing, recontributing some heat to the body. This inefficiency is compensated for by an increase in the total amount of secretion. During subsequent rest periods the moisture which has accumulated in the clothing is slowly reevaporated, increasing the loss of heat from the body at a time when maximum conservation of stored heat is necessary.

A thermostatically controlled, electrically heated dummy "man" has been dressed in an Arctic outfit and exposed at 0°F. in an effort to determine the extent to which reevaporation from the clothing may increase body heat loss. When 1300 grams of moisture (a reasonable sweat secretion) were put into the underwear and socks daily for 10 days about 18 Cals./m<sup>2</sup>/hr. were continuously taken from the body for evaporation. This is three times the usual heat loss from insensible perspiration, and results in a 50% increase over the dry clothing requirement of a sitting man.

In the case of men working hard (6-7 times basal) at 0°F. it was found possible to reduce sweating from the rate of 350 to 400 grams an hour to as little as 50 grams per hour by reducing the costume from a standard Arctic uniform to long underwear, socks and shoes. "Underdressing" to this extent certainly is not practical, but men can reasonably be expected to "underdress" during work at low temperatures to the point where sweat secretion is only 100 to 200 grams per hour.

**The response of the vasomotor center to the**

direct action of hypoxia. THEODORE BERNTHAL and CLARENCE C. WOODCOCK, JR. (by invitation). *Dept. of Physiology, Vanderbilt Univ., School of Medicine, Nashville, Tenn.* The responses of the vasomotor center to hypoxia were recorded during the absence of all known chemoreceptor support. Changes in activity of the vasomotor center were indicated by changes in arterial blood volume flow in the foreleg. Local hypoxia at the leg was prevented and the driving head of arterial blood pressure was maintained constant there so that the initiation of changes in blood volume flow in the leg was dependent exclusively upon nervous factors. The experimental animals were anesthetized dogs.

In 3 of 10 animals, inhalation of gas mixtures ranging from 0 per cent to 7 per cent in oxygen content produced only diminution of blood flow in the leg, indicating predominance of excitatory action of hypoxia at the vasoconstrictor center. In 6 of 10 animals the responses were mixed, i.e., centrogenic vasodilatation was produced by lesser degrees of hypoxia (6-10 per cent O<sub>2</sub> inhalation) and vasoconstriction by more intense hypoxia, or vasoconstriction and vasodilatation alternated during the course of a single response. In 1 animal, only centrogenic vasodilatation resulted from hypoxia.

The results suggest two separate but simultaneous effects of hypoxia on the vasoconstrictor center, one depressant and one excitatory, with a varying balance between them. In general, responses in which excitation dominated were more frequently encountered than were the converse. The threshold intensity of hypoxia for centrogenic vasoconstriction was very much greater than that for reflexogenic hypoxic vasoconstriction.

**Equilibrium and susceptibility to seasickness.<sup>1</sup>** LT. (jg) J. E. BIRREN, H(S), USNR (introduced by H. F. Blum). *Naval Medical Research Inst., Bethesda, Md.* Studies of the basis for susceptibility to seasickness were initiated by observations on 48 men who were so susceptible to seasickness that they were unable to work effectively at sea. These men were given a series of tests, three of them involving equilibrium; the Barany Chair, the ataxiograph, and the railwalking test.

The susceptible men were not different from normal seamen in their ability to balance themselves in the railwalking test, which requires the subjects to walk a ten foot one-inch wide rail. Postrotational nystagmus was slightly but not significantly longer in the susceptible men for both the horizontal and vertical positions in the Barany Chair. The falling reaction to the vertical position appeared exaggerated in several of the susceptible men. The Barany Chair test as a whole did not bring out any

<sup>1</sup>The opinions and views set forth are those of the writer and are not to be considered as reflecting the policies of the Navy Department.

striking differences between the normal and the susceptible men.

A marked difference appeared between the susceptible and normal men in the amount of body sway. Thirteen of the seasick group were over three standard deviations from the mean of the normal population; such extreme cases can be expected to occur in 0.15 per cent of the normal population. The observed correlation between susceptibility to seasickness and marked body sway may be related to the long history of motion sickness noted in the susceptible men.

**Individual differences in natural and artificial protection against sunburn.<sup>1</sup>** HAROLD F. BLUM and W. S. TERUS (by invitation). *Naval Medical Research Inst., Bethesda, Md.* The corneum acts as a semi-opaque filter for radiation of wavelengths of the erythema-spectrum, and thus provides protection against sunburn of the skin. A superimposed semi-opaque layer covering the skin, e.g., a sunburn preventive ointment, gives additional protection. For optical reasons the protection afforded by such an additional layer, against spectrally inhomogeneous radiation such as sunlight, should vary with the opacity of the corneum as well as that of the superimposed layer. We have found that the degree of protection afforded by a given sunburn preventive varies in a regular manner with the erythema threshold of the individual. This demonstrates that the individual erythema threshold is largely determined by optical factors, principally the opacity of the corneum, since differences in other factors would not produce such variation. Variation in the protection afforded among individuals has been a source of confusion in estimating the efficacy of sunburn preventives.

**Electromyographic studies of innervation patterns of muscles under conditions of voluntary innervation.** J. F. BOSMA (introduced by E. Gellhorn). *Univ. of Minnesota.* Electromyographic studies were made of the function of the triceps and biceps muscles of eight subjects through surface electrodes. Recordings were made by an Offner ink-writing crystograph.

Under conditions of slight and moderate exertion a difference was found in the electromyogram of triceps and biceps. That of the triceps consisted predominately of simple, brief waves (60 to 90/sec.). Some of these waves were grouped into characteristic innervation units of 4 to 8 similar consecutive waves. The electromyogram of the biceps consisted chiefly of slow composite waves with a frequency of 30 to 40 per cent of that of the triceps. These patterns were confirmed by the cathode ray oscillograph. The difference in the electromyograms of these two muscles was suffi-

cient to distinguish triceps and biceps innervation in unfamiliar records.

Under conditions of slight extension, little or no potentials appear in the biceps. With increased function of the triceps its pattern appears in the biceps to an increasing degree. In a similar manner the biceps pattern of innervation appears in the triceps muscle in direct relation to the strength of the biceps contraction. There is synchrony of a varying proportion of these waves in the agonist and the antagonist.

The electromyograms indicate basic differences in the innervation patterns of biceps and triceps. The appearance of the biceps pattern in the triceps in flexion suggests an irradiation of the pattern of the biceps innervation into the neurons involved in the innervation of the triceps.

**The action potentials of visceral smooth muscle.** EMIL BOZLER. *The Dept. of Physiology, Ohio State Univ., Columbus.* Potentials were recorded during spontaneous rhythmic contraction in isolated intestinal strips and from organs *in situ* in anesthetized animals. Differential leads with a distance of about 1 mm. were usually used. Monophasic potentials confirmed the validity of the results obtained. As previously found for the ureter, the potentials of the stomach and intestine, in most species, have a long plateau, giving rise to a sharp R-wave and a slow T-wave in differential records. In the intestine, spikes are superimposed on the plateau during strong contractions but, if the contractions are weakened by cooling or adrenalin, the potentials assume their simplest form and become indistinguishable, except for their longer duration, from those of cardiae muscle. The guinea-pig is exceptional because all its smooth muscles studied so far, including the ureter, give potentials consisting chiefly of bursts of brief spikes.

High concentrations of adrenalin stop the action potentials and motility but, with smaller amounts of the drug, rhythmic potentials may be present while contractions are not detectable visually. In experiments on isolated intestinal strips, using a sensitive muscle lever for recording contractions, it was found, however, that each potential was followed by a contraction. The magnitude of the electric change diminishes only slightly when the mechanical response decreases many times.

**The nature of respiratory activity produced by intravenous injection of ammonium chloride.** CHARLES R. BRASSFIELD, ELWOOD T. HANSEN (by invitation) and ROBERT GESELL. *Univ. of Michigan.* Intravenous injection of ammonium chloride produces changes in breathing very similar to those resulting from the administration of eserine. Breathing becomes slower and irregular in rhythm and depth. In the deep respirations both inspiratory and expiratory contractions are stronger than normal. In many of the weaker

<sup>1</sup> The opinions and views set forth herein are those of the writers and are not to be considered as reflecting the policies of the Navy Department.

breaths only expiration is intensified. The sustained potentiation of activity of the expiratory half-center would seem to be a plausible cause for the retardation of breathing. The great power and extreme brevity of the deeper respirations add strong evidence for the excitatory nature of the vagal respiratory reflexes (Gesell, Worznak, Moyer and Hamilton). Furthermore, they indicate a marked potentiation of the inspiratory and expiratory vagal reflexes, for when the vagus nerves are cold blocked the sustained expiratory activity disappears, breathing becomes regular in height and frequency and inspiration transpires at a much slower velocity. The results obtained with cold blocking of the vagi are similar to those obtained in eserine poisoning.

It is tentatively proposed that the increased anticholinesterase activity existing during ammonium chloride acidosis and eserine poisoning may be the main cause underlying the similarity of changes in breathing occurring under these conditions. Whether the ammonium radical exercises an additional effect remains to be determined.

CO<sub>2</sub> breathing and carbohydrate involvement in anoxia. S. W. BRITTON and R. F. KLINE (by invitation). *Dept. of Physiology, Univ. of Virginia Medical School, Charlottesville.* Rats were studied in chambers at 162 mm. Hg barometric pressure (37,000 ft. alt. equivalent) with continuous ventilation. Differences in male and female response were noted.

Pre-exposure of animals to a CO<sub>2</sub>/O<sub>2</sub> (15/85) mixture resulted in greatly increased resistance to anoxia. In many cases survivals were two to four times as long after such treatment. Differences were more marked in fed than in fasted rats.

Glucose administration was more effective than CO<sub>2</sub> breathing in prolonging survival under severe anoxia. In some cases carbohydrate-treated animals lasted one to two hours longer than normal controls. Related were the severe convulsions invariably observed in fasted animals exposed to anoxia, and the absence of seizures in fed rats with higher blood glucose levels. Tissue glycogen as well as blood glucose values were studied, and the effects of various hormones were tested.

A study of the effect of hypothalamic lesions on the eating habits of rats. CHANDLER McC. BROOKS, RICHARD A. LOCKWOOD (by invitation) and MILTON L. WIGGINS (by invitation). *Dept. of Physiology, School of Medicine, The Johns Hopkins Univ., Baltimore.* The times of eating and the quantity of food consumed at each meal were determined in rats fed *ad libidum*. All rats studied, when normal, ate approximately 70 percent of their daily food intake at night (6 p.m. to 6 a.m.). During the day they ate, on the average, once every 3 to 4 hours. At night the frequency was once every 1 to 2 hours. The maximum meal size rarely ex-

ceeded 4 grams of mash and the average was 1.5 to 2 grams. Day and night meals did not vary significantly in size. Surgical reduction of stomach capacity caused a greater frequency of eating and a smaller meal size until the organ had again attained a normal capacity. Hypothalamic lesions of the type which produce obesity reversed the period of maximum food consumption. During the dynamic phase of obesity animals habitually ate an enormous meal (14 to 20 grams) immediately after the food container was filled with fresh food. This resulted in a daylight consumption of approximately 65 per cent of the day's food. Throughout the remaining hours they ate at rather uniform intervals of once every 2 hours. The average meal size was 4 to 7 grams. As the static phase was attained patterns of eating tended to revert to the normal. At night 56 per cent of the food was eaten; meal size averaged 3 to 4 grams; the average frequency of eating was once every 2.5 to 3 hours during the day and once every 2 hours at night.

A study of the respiratory quotient in obesity. CHANDLER McC. BROOKS. *Dept. of Physiology, School of Medicine, The Johns Hopkins Univ., Baltimore.* A study was made of the effect of food (Purina dog chow) ingestion on the respiratory quotient of rats when normal and at various times during the dynamic and static phases of the obesity produced by hypothalamic lesions. It was found that abnormally high quotients occurred throughout the dynamic phase but not during the static phase. The rise above unity was not obtained unless three grams or more, dry weight, of food were ingested. Larger quantities caused a slightly higher rise but chiefly a prolongation of the period of high R.Q. The rise was detectable 60 minutes after eating a 4 to 6 gm. meal and the peak was attained within two hours. Within four hours the R.Q. generally fell to or below the pre-feeding level. Ingestion of 5 to 8 cc. of olive oil did not cause the R.Q. to rise above unity in three rats which showed the typical change after eating the carbohydrate-containing food. Although ingestion of food did not cause the R.Q. to rise above unity immediately after operation the phenomenon was present by the fourth day. Six animals, with effective lesions, were pair-fed to normal rats but were given their total ration subdivided into small quantities, which never exceeded two grams. These portions were delivered to the rats at regularly spaced intervals. In these rats, when given a test meal, the respiratory quotient rose well above unity. Thus the phenomenon developed although periodic engorgement with food had never occurred.

Electrode potential measurements of *Penicillium notatum*. MATILDA MOLDENHAUER Brooks. *Univ. of California, Berkeley.* To find some evidence for the interpretation of the action of *Penicillium notatum* in certain diseases, measurements

were made of the Eh and the pH of corn steep broth in which it was grown. The broth alone had an Eh of -.028volts at pH 3.65 initially as measured by the Coleman electrometer. After inoculation in 2 weeks the Eh was -.258 and the pH 8.4. In order to reduce these values to comparable terms, making certain assumptions, the rH was calculated as  $2 \text{ pH} + \frac{\text{Eh}}{.03}$ . *Penicillium* under aerobic conditions changed the rH of the medium from 6.4 to 8.5. Purified penicillin, 100,000 Oxford units in saline (Parke, Davis), registered an Eh of -.128 at pH 6.5 and an rH of 8.7. Flasks tightly stoppered gave slight growth; the Eh was -.183 at pH 3.8 and an rH of 1.5. When .006 M KCN was added aerobically, the Eh was .178, the pH 3.65 and the rH 1.4. No growth obtained. Other organisms used for comparison were *Saccharomyces cerevisiae*, *Torula utilis*, *Mycoderma* and *Aspergillus flavus* grown in other media. These produced negative Eh values but low pH and rH values. Clifton (1933) determined the Eh of *Staph. aureus* as -.15 at pH 8.0, giving an rH of 11.

It seems therefore, that the redox potential at a favorable pH value, of purified penicillin, or of the products of metabolism of the growing organism itself, may poised the potential in a region unfavorable for the growth of such organisms as *Staph. aureus*.

**Changes in psychomotor performance in bed-rest.<sup>1</sup>** JOSEF BROZEK (by invitation), HAROLD GUETZKOW (by invitation) and ANCEL KEYS. *Laby. of Physiological Hygiene, Univ. of Minnesota*. The effects on motor performance of 3 weeks of hospital bed-rest were investigated in 6 normal young men. In a preliminary standardization period the subjects were brought to a steady plateau of performance in a series of tests of strength, speed, movement coordination and postural coordination. Measurements were made daily during the first week of recovery after bed-rest and were repeated 3 weeks later, without practice in the interim.

Performance was substantially unaffected by mere cessation of practice but 3 weeks of bed-rest produced significant deterioration in postural and complex motor coordination. In percentage of control performance before bed-rest, postural steadiness (ataxiameter) averaged 70, 88, 94 and 95 on successive days after bed-rest. Similarly, eye-hand-foot coordination averaged 84, 85, 94 and 100%, respectively, for the first 4 days out of bed. Back strength (back-lift dynamometer) showed less deterioration; on the first 4 post-bed rest days the values averaged, respectively, 93, 92, 95 and 97%.

of the control. Bed-rest had a similar slight effect on the speed of gross body movements. Neither strength of grip nor speed of small hand movements (tapping alternate plates) showed any deterioration in bed-rest.

One man was later subjected to an inguinal herniorrhaphy and remained in bed for 3 weeks. Recovery followed a similar course. Postural steadiness, as percentage of control, was 69, 77, 79 and 91 on the first 4 days after simple bed-rest, and 72, 85, 94 and 98 in post-operative conditions.

**Assay of pepsin in human urine.<sup>1</sup>** GLADYS R. BUCHER (introduced by R. Hafkesbring). *Dept. of Physiology, Woman's Medical College of Pennsylvania, Philadelphia*. The hemoglobin method has been adapted to the assay of pepsin in human urine. A pepsin has been found in all urine samples from 25 female subjects. Storage of the urine for 4 days at 15°C does not alter the peptic activity. The pepsin concentration in any single sample correlates well with its specific gravity.

Volume, pH, specific gravity and pepsin were determined in 218 samples of 24-hour urine collections. The subjects, 10 student nurses, whose fasting gastric secretion contained pepsin, made their own collections for 6 days a week during one menstrual cycle. They kept a record of their food and fluid intake.

Highest peptic potencies occurred in specimens with low pH, (4.5-5.0). When the pH was 7.0 or more, little or no pepsin was found. There was positive correlation between the pepsin concentration and the specific gravity. The average pepsin concentration of 211 specimens (pH 4.0-6.9) was 0.439 mg. tyrosine per cc. when digested for an hour. In this study no relationship appeared to exist between gastric and urinary pepsin concentrations. The average potency of the gastric secretions was 6.37 mg. tyrosine per cc. when digested 7.5 minutes.

The total 24-hour urine pepsin output on all specimens averaged 296.8 mg. tyrosine. Individuals showed considerable daily fluctuations for which an explanation has not yet been found. In spite of this, the average 24-hour output of 80% of 10 subjects fell within the range of 200-400 mg. of tyrosine.

**Abolition of tremor by removal of area γ.** PAUL C. BUCY. *Illinois Neuropsychiatric Inst. and the Dept. of Neurology and Neurological Surgery, Univ. of Illinois College of Medicine*. In various ways it has been previously demonstrated that tremor at rest (parkinsonian tremor) is abolished by destruction of the contralateral precentral motor cortex or of the pyramidal tract arising from it. Exactly which part of the precentral motor

<sup>1</sup>This work was supported in part under the terms of a contract between the Regents of the University of Minnesota and the Office of Scientific Research and Development. Support from other sources will be acknowledged in final publication.

<sup>1</sup>Aided by a grant from the Committee on Therapeutic Research, Council on Pharmacy and Chemistry, American Medical Association.

cortex was concerned with the production of tremor was, however, unknown. On Aug. 3, 1943 area 4γ, the area giganto-pyramidalis which lies in the posterior part of the precentral gyrus, was removed from the left cerebral hemisphere of a 23-year-old man. This patient had suffered from weakness and a severe tremor involving the right extremities for a period of 15 years, following an illness at the age of 5½ years. This illness was presumably an encephalitis. At the time of the operation a suppressor area, thought to be area 4s, was demonstrated just anterior to the precentral sulcus. Following the extirpation the tremor was abolished and has remained so. There was also a considerable paralysis, particularly of the hand and fingers and some increase in spasticity. There was a temporary disturbance of sympathetic activity and a delayed temporary disturbance in sensory perception. This observation indicates that tremor at rest results from nervous impulses arising from the Betz cells and transmitted to the spinal cord by the large (9 to 22 $\mu$ ) fibers which arise from the Betz cells and form only 2 to 3 per cent of the pyramidal tract.

**Evaluation of the 2-6 hour rat pregnancy test.**  
**CARL A. BUNDE.** *Dept. of Physiology and Pharmacology, Southwestern Medical College, Dallas, Texas.* Ovarian hyperemia of the immature rat as an end point in a rapid test for pregnancy has been reported by several investigators. There is no general agreement on the reliability of the test. Results reported here are concerned with evaluation of the test as well as an attempt to discover sources of error and thus increase the accuracy. A comparison was made of (1) subcutaneous injection with examination at the end of 6 hours, (2) intraperitoneal injections with examination of the ovaries 2 hours later, and (3) a modification combining (1) and (2). Tests on 83 urines showed no significant difference among the 3 methods. With 82 urine samples, using 2 rats for each, 81% were diagnosed correctly. In 61 tests, using 3 rats, 90% were diagnosed correctly. This percentage accuracy was increased when urines of low specific gravity were discarded.

Pituitary gonadotrophins and pregnant mare serum as well as chorionic gonadotrophin were found to give positive responses. Therefore, urines from female castrates, women during menopause, and young women at the time of expected ovulation were tested. Of 16 such patients, 2 gave a positive reaction. The minimal amount of chorionic gonadotrophin which would produce ovarian hyperemia was found to be 15 to 25 i.u. Large amounts of estrogens produced no ovarian hyperemia. (Urines and clinical data were obtained through Dr. W. F. Mengert, Department of Obstetrics and Gynecology.)

**Scalp potential, an index to brain potential.**

**W. E. BURGE.** *Dept. of Physiology, Univ. of Illinois, Urbana.* One nonpolarizable electrode was placed on the exposed gastrocnemius muscle, which served as a point of reference, of an etherized dog, while the other electrode, with a potentiometer in the circuit, was placed alternately on the exposed motor area of one side of the brain and on the shaved scalp overlying the motor area of the opposite side.

When the dog was lightly anesthetized, sufficiently to prevent pain, the scalp was found to be weakly positive to the gastrocnemius, the point of reference, and the underlying brain cortex strongly negative, with an average positive potential of the scalp in the ten dogs used of 1.9 millivolts and an average negative potential of the brain cortex of 15.2 millivolts, or a 1 to 8 ratio between scalp and brain potential.

Increasing the depth of anesthesia, decreased both the positive potential of the scalp and the negative potential of the underlying brain cortex, and in deep anesthesia both fell to the zero level. During recovery from anesthesia, both the positive potential of the scalp and the negative potential of the underlying brain cortex rose practically to their previous high levels.

Since the positive potential of the scalp fluctuates with the negative potential of the underlying brain cortex, scalp potential may be used as an index to brain potential. An increase in the positive potential of the scalp indicates a rise in the negative potential of the underlying brain cortex and decrease indicates a fall in brain potential.

A lowering of the negative potential of the motor area of the brain during physical exertion as a cause of muscular fatigue. **W. E. BURGE** and **R. A. PURDY** (by invitation). *Dept. of Physiology, Univ. of Illinois, Urbana.* When one platinum electrode was placed on the forehead and another on the forearm, with a potentiometer in the circuit, the scalp of the forehead was found to be positive to the forearm when the subjects were at rest with an average positive potential of 48 millivolts in the 20 subjects used.

Exercise, by running at top speed up and down four flights of stairs in rapid succession to fatigue and exhaustion, decreased the positive potential of the scalp to the zero level, and during subsequent rest the potential rose practically to its previous high level.

We found in etherized dogs that the scalp was positive and the underlying brain cortex negative and that the positive potential of the scalp fluctuated with the negative potential of the underlying brain cortex, so scalp potential may be used as an index to brain potential. Hence, the fall in the positive potential of the scalp of humans during muscular fatigue and exhaustion indicated a fall in the negative potential of the underlying motor

cortex, and the rise during subsequent rest indicated a rise in the negative potential of the underlying brain cortex.

These observations suggest that the site of muscular fatigue is the motor area of the brain, and its cause a fall in the potential of the motor area to the same level as that of the outlying muscles, so that under these conditions no negative charges or nerve impulses can pass to the muscles to stimulate them to contract.

**Voluntary movement in relation to brain potential.** W. E. BURGE. *Dept. of Physiology, Univ. of Illinois, Urbana.* When one nonpolarizable electrode was placed on the exposed motor area of the brain of an etherized dog and another on the exposed gastrocnemius muscle, with a potentiometer connected in the circuit, the motor cortex was found to be negative to the muscle when the dog was only lightly anesthetized, sufficiently to prevent pain, and could make slight spontaneous movements with an average negative potential of 18.4 millivolts in the fourteen dogs used.

Increasing the depth of anesthesia decreased the negative potential of the brain cortex along with the decrease produced in the ability of the dog to make voluntary movements, and in deep anesthesia when the dog was no longer able to make spontaneous movements, the potential of the motor area had dropped practically to the same level as that of the muscle. Decreasing the depth of anesthesia increased the negative potential of the motor cortex, and when the dog had sufficiently recovered to make slight spontaneous movements, the grain potential had risen practically to its previous high level.

Hence it would seem that a necessary condition for the flow of negative electric charges or nerve impulses from the motor area out over motor nerves to the muscles to produce voluntary contraction is the same in the living animal as for the flow of electrons in a purely physical system, namely, that the motor area be at a higher level of negative potential than that of the outlying muscles.

**Use of the dye method in plasma volume determinations in anoxia.** D. BAILEY CALVIN. *Dept. of Biological Chemistry, Univ. of Texas, School of Medicine, Galveston.* Marked cell concentration and potassium increases occur in shock due to anoxia and asphyxia (Am. J. Physiol. 124: 192, 1938). The same degree of hemoconcentration is not shown by plasma protein estimations.

To obtain further evidence on the nature of blood changes in shock, attempts were made to determine plasma volume using T-1824 and the dye method described by Gregersen, and by Gibson. Interpretations of the data are difficult. Whereas changes in the cellular elements of the blood indicate marked hemoconcentration, plasma volume changes are of a much smaller degree. The results

obtained are quantitatively similar to those calculated from increases in plasma proteins.

As previously reported, under the conditions of these experiments, the albumin: globulin ratio increases, along with the increase in plasma protein concentration, but to a somewhat greater extent. The interpretations of these data, including those on plasma volume measurements using the dye method, would indicate a marked loss of relatively unchanged plasma from the vascular system. It is reasonable to assume that the anoxia causes an increased capillary permeability by which plasma, plasma proteins (especially albumins) and the injected T-1824 dye are lost from the circulation at a rapid rate. (J. F. Danielli and A. Stock, Biol. Rev. Cambridge Phil. Soc. 19: 81, 1944.)

Under the conditions of these experiments the dye method does not give entirely satisfactory values for plasma volume. Cell volume or hemoglobin determinations appear to be better criteria for estimating changes in blood volume in the shock due to anoxia.

**Further studies of estrogen-sodium dehydrocholate solutions.** A. CANTAROW, K. E. PASCHKIS, A. E. RAKOFF (by invitation), A. A. WALKLING (by invitation) and L. P. HANSEN (by invitation). *Jefferson Medical College, Philadelphia, Pa.* A number of steroids and other substances practically insoluble in water go into solution rather readily in aqueous solutions of sodium dehydrocholate. Previous observations suggest that this phenomenon is not due to the operation of purely physical forces, but, at least in the case of estrone, to the formation of a rather firm complex with the bile acid (Endocrinol. 35: 129, 1944). This view has received support from the results of diffusion studies and of studies of the rate of excretion of estrogen in the bile of bile-fistula dogs after intravenous injection of alpha-estradiol in (a) 95% alcohol solution, (b) sodium dehydrocholate solution and (c) 95% alcohol solution followed by injection of sodium dehydrocholate. The excretion pattern after injection of the estrogen-dehydrocholate solution differed from that after separate administration of the estrogen and dehydrocholate solutions in such manner as to suggest some form of firm combination of the estrogen and the bile acid.

**A trap with holder for handling vicious laboratory animals such as wild rats.** EMMETT B. CARMICHAEL, RALPH McBURNEY (by invitation) and LOUISE RICKEMAN CASON (by invitation). *Depts. of Physiological Chemistry and Bacteriology, School of Medicine, Univ. of Alabama, University.* The apparatus consists of a holder, and a cone-shaped tunnel or trap which is soldered to a sheet iron shield, and two metal comb-like stops. The holder and trap are made of hardware cloth. The trap is a truncated cone with a sheet iron collar soldered to the truncated end over which the cylindrical holder

fits. The holder is tapered at the extreme end. One stop is for use with the trap and the other is for the holder. The shield of the apparatus can be placed over the open door of a small cage. Then the animal usually can be stimulated to enter the tunnel by simply blowing into the rear of the cage. The first stop is placed next to the opening in the cage. As the animal enters the holder the other stop is put in place behind it. The holder with the animal can be removed from the trap and the animal can be handled with ease for such procedures as weighing, feeding, taking blood, and injections with absolute protection to the operator.

The effects on temperature regulation in rats injected with rattlesnake venom. EMMETT B. CARMICHAEL. *Dept. of Physiological Chemistry, School of Medicine, Univ. of Alabama, University.* Adult rats were injected subcutaneously with rattlesnake venom, and after 30 minutes some animals were placed in an incubator at 92-96°F. and others were placed in a refrigerator at 52-56°F. The rectal temperatures were taken before the injection of venom and again just previous to subjecting the animals to one of the above temperature ranges. The body temperatures were also taken 3 hours, 8 hours, 24 hours, 48 hours and 72 hours after the injections when the animals lived that long. The results on the rats that survived may be tabulated as follows:

No. of rats	Normal temp. rats	Temp. treated at	Body temperature after injection of rattlesnake venom					
			30 min.	3 hr.	8 hr.	24 hr.	48 hr.	72 hr.
C.	F.	C.	C.	C.	C.	C.	C.	C.
14	38.68	92-96	36.38	39.46	38.76	38.49	36.16	37.13
9	38.53	52-56	39.55	36.85	36.77	37.15	35.06	38.32

The lowering of the body temperature seemed to be helpful since 50 per cent of the rats survived an injection of 32.5 mgm. of rattlesnake venom per kgm. while 100 per cent of the animals died when subjected to the higher temperature range after receiving only 26 mgm. of venom per kgm.

Effect of high oxygen tension on carbon dioxide production by frog muscle. RUTH ELIZABETH CASS (introduced by W. O. Fenn). *Dept. of Physiology, School of Medicine and Dentistry, Univ. of Rochester, Rochester, N. Y.* The object of the present study was to investigate the effect of high O<sub>2</sub> tensions on the CO<sub>2</sub> production of isolated tissues.

The CO<sub>2</sub> output of frog sartorii was measured by the conductivity method, with one muscle exposed to O<sub>2</sub> at 100, 200, 300 or 500 pounds gauge pressure and the contralateral muscle of the same frog run as a control in O<sub>2</sub> at atmospheric pressure. Following the application of high O<sub>2</sub> pressure the rate of

CO<sub>2</sub> production increased initially, but decreased subsequently to a small fraction of the resting rate. The greater the pressure used, the earlier the decline in rate of CO<sub>2</sub> output. After release of excess pressure the rate of CO<sub>2</sub> production increased to or above the resting rate, but could be lowered a second time by reexposure of the muscle to high O<sub>2</sub>.

When the pressure on muscles in 100 per cent O<sub>2</sub> was raised to 300 or 500 pounds with N<sub>2</sub> no decline in CO<sub>2</sub> output appeared. If 500 pounds total pressure was used, of which 200 or 300 pounds was O<sub>2</sub> and the remainder N<sub>2</sub>, the CO<sub>2</sub> production was similar to that with 200 or 300 pounds O<sub>2</sub> pressure alone. Clearly the O<sub>2</sub> tension and not the total pressure was the determining factor.

Acidification released similar quantities of CO<sub>2</sub> from O<sub>2</sub>-poisoned and control muscles, indicating that there was no accumulation of CO<sub>2</sub> within the poisoned muscles.

Influence of specific gravity and rate of decompression on bubble formation in rabbits decompressed to altitude.<sup>1</sup> LT. (jg) H. R. CATCHPOLE and LT. I. GERSH, USNR (by invitation). *Naval Medical Research Inst., Bethesda, Md.* Bubble incidence in two groups of rabbits decompressed to 45,000 feet equivalent altitude in 3 to 30 seconds and in 2 to 7 minutes showed no constant relationship to body fatness or leanness as determined by the specific gravities of the animals. Decompression time is a determining factor affecting bubble formation. Maximal bubble incidence and early death are associated with rapid decompression; minimal bubble formation and later death with slow decompression.

A critical decompression rate of 10 minutes to 45,000 feet was established below which 85% of the animals die with vascular bubbles in 30 minutes or less and at which 85% survive for 30 minutes after reaching altitude.

Histological and hormonal changes in the neurohypophysis of rats following NaCl administration. GEORGE H. CHAMBERS (introduced by Kendrick Hare). *Dept. of Physiology, State Univ. of Iowa, Iowa City.* Since the intravenous or oral administration of hypertonic salt solutions releases large amounts of pituitrin, we examined the pituitrin content and the histological appearance of the neurohypophysis of control and salt treated rats. Salt was injected intravenously in 0.9 and 5.0% solution or added to the drinking water so that the concentration was systematically elevated 0.5% every second week until a maximal concentration of 2.5% was provided. The colony of 65 rats used was divided so that control and experimental groups for each procedure contained rats

<sup>1</sup> The opinions expressed in this article are those of the writers, and are not to be construed as reflecting the official views of the Navy Department or of the Naval Service at large.

of the same age, weight and sex. It was found that the injection of salt increased the pituitary weight: body weight ratio and produced an edema of the neurohypophysis. When a high salt intake was forced for 5 weeks the pituitary weight:body weight ratio was not altered, but the hormonal content of the neurohypophysis, as assayed on dogs with diabetes insipidus, was greatly reduced.

**Visible spectral absorption of reduced luciferin.** AURIN M. CHASE. *Physiological Laby., Princeton Univ., Princeton, N. J.* Measurements of the visible absorption spectrum of aerobic solutions (pH 6.8) of doubly-purified *Cypridina* luciferin (i.e., carried through two cycles of purification by Anderson's method) show an initial absorption band at 435 m $\mu$ , which is rapidly replaced by one at 465 m $\mu$ . The latter then disappears slowly, leaving the solution practically colorless (Chase, *J. Biol. Chem.*, 1943). The 435 m $\mu$  band was assumed by Chase to represent luciferin in a non-oxidized condition. However, since the spectrum could not be measured until several minutes after the luciferin had been exposed to oxygen in the solvent, this band might equally well be attributed to small amounts of oxidized luciferin. Because of the importance of the absorption spectrum—and of the changes which it undergoes—as a possible means toward determining the structure of luciferin, it is necessary to decide what state of the molecule this visible absorption band represents.

This question has been answered through a comparison of the absorption spectra of three kinds of luciferin solutions; (1) doubly-purified luciferin measured in an aerobic solvent, (2) singly-purified luciferin measured in an aerobic solvent and (3) singly-purified luciferin dissolved and measured in complete absence of oxygen. By appropriate treatment of the data it can be shown that the 435 m $\mu$  absorption band is not due to reaction with dissolved oxygen in the solvent during the short interval before the spectrum is measured. Rather, it exists even though the luciferin has had no contact with oxygen and is, therefore, a property of reduced luciferin.

**Effects of sex hormone therapy on a prepubertal male castrate chimpanzee.** GEORGE CLARK. *Yerkes Labs. of Primate Biology, Orange Park, Fla.* A male chimpanzee, now almost 11 years old, was castrated at the age of 22 months. As compared with the available normal material few or no deviations were found either in bodily or sex behavior development. Under androgenic therapy there was a decrease in the number of copulations per hour, ejaculation and an increase in dominance, while the latter decreased with an estrogen. No significant weight changes occurred during the periods of treatment with sex hormones, and skeletal findings await control data. These results are discussed in relation to current ideas of the effects of prepubertal castration in the human.

**Observations on histamine release from tissues during anaphylaxis.** SUE CLOYD (by invitation) and W. A. SELLE. *Dept. of Physiology, Univ. of Texas, Medical School, Galveston.* According to the humoral theory of anaphylaxis, histamine is released from sensitized cells during the antigen-antibody reaction. Evidence for this is chiefly circumstantial. Experiments have been carried out to determine whether histamine is liberated from intestinal segments, minced intestine, lung, and liver of guinea pigs sensitized to egg white and horse serum. Isolated strips (ileum) of normal starved guinea pigs, sensitive to .5 gamma of histamine, were used as test tissues. The individual segments were placed in 50 cc. Berkfeld filter tubes and perfused with oxygenated Tyrode's solution. Following a short interval for stabilization of the spontaneous contractions, 2-4 grams of sensitized tissues were introduced to the perfusion fluid. After another interval for stabilization of the test tissue, the bath containing the sensitized and normal (test) tissue was charged with the antigen used in the sensitizing injection.

Although the addition of sensitized tissue frequently resulted in a slightly greater increase in tonus than did the addition of normal tissue, the shocking dose of antigen was not followed by a significant response in the test tissue. The fluid bathing the strips was then further tested for histamine by the method of Barssoum and Gad-dum. There was no evidence obtained by this method either that the histamine content of the perfusing fluid is significantly increased during the Schultz-Dale reaction.

**The sequence of physiologic events in man during exposure to positive acceleration.**<sup>1</sup> C. F. CODE, E. H. WOOD, R. E. STURM (by invitation), E. H. LAMBERT (by invitation) and E. J. BALDES. *Acceleration Laby., Mayo Aero Medical Unit, Rochester, Minn.* There is a definite sequence to the physiologic events that occur in the comfortably seated human being during exposure to positive acceleration. This sequence is divided into two distinct periods: the period of progressive failure and the period of compensation.

During the period of progressive failure, the pulse rate progressively increases, the amount of blood in the ear is progressively reduced, the pulse in the ear may be gradually reduced or abruptly lost, the blood pressure at the level of the base of the brain declines and reductions of vision and consciousness, if they occur, become evident. As accelerations of greater intensity are experienced, the extent of these changes is increased.

The period of progressive failure is usually terminated by compensatory reactions, which become

<sup>1</sup> Work done under contracts with: (1) United States Army Air Forces, Wright Field, Dayton, Ohio, and (2) the Office of Scientific Research and Development, National Research Council, Washington, D. C.

effective about six to eleven seconds after the onset of acceleration.

During the period of compensation, the blood pressure rises, the ear pulse may return or increase, the amount of blood in the ear increases, the pulse rate increase is checked and the pulse may slow and, if these compensatory changes are sufficiently effective recovery from symptoms (both loss of vision and consciousness) will occur.

This consistent pattern has been observed in a total of more than 250 subjects. Measurement of the magnitude of the changes has allowed the development of an accurate quantitative assay procedure for the determination of man's g tolerance and for the measurement of the efficacy of any device designed to prevent or offset these physiologic changes.

**Hydrostatic anti-blackout protection; the protection afforded man against the effects of positive acceleration by immersion in water (motion picture).** C. F. COPE, E. H. WOOD and E. J. BALDES. *Acceleration Laby., Mayo Aero Medical Unit, Rochester, Minn.* The motion picture shows the methods used in this study and illustrates the average protection afforded man against the effects of positive acceleration by immersion in water.

The study was carried out on the human centrifuge. A specially constructed bath tub was placed in the gondola or cockpit of the centrifuge. The subjects sat in this tub in the same position as that assumed by a pilot in a fighter airplane. Each test included the determination of the subject's g tolerance while sitting in the tub—first, without water, then with water added to various body levels, and finally again without water as a recheck of the control determinations. On the average, immersion in water to the xyphoid gave 0.9 g protection and immersion in water to the level of the third rib gave 1.7 g protection.

**Graphic registration of arterial systolic and diastolic pressure in animals.** OTIS M. COPE. *Dept. of Physiology and Biochemistry, New York Medical College, Flower and Fifth Avenue Hospitals.* This method is based on the principle of recording by means of mirrors mounted on a lever and rubber diaphragms, the actual movement of the manometer and the fluctuations in blood pressure through the registration of the Korotkoff sounds. By connecting any one of these levers to which the mirror is attached with a heart muscle preparation or excised arterial or intestinal strips it is possible to get a record in which friction is reduced to a minimum of tonus waves and the effect of perfusion fluids containing test substances on these preparations.

**Pancreatic diabetes in the calf.** ELLEN T.

COOK (by invitation) and J. A. DYE. *Dept. of Physiology, Cornell Univ., Ithaca.* Total pancreatectomy was successfully accomplished in 2 out of 3 month-old calves. The resultant diabetes resembled that observed in goats and hypophysectomized dogs (Lukens, Am. J. Physiol. 122: 729, 1938). Moderate hyperglycemas which varied roughly quantitatively with the food intake (milk) developed, during fasting the blood sugar values dropped to levels below those for fasting normal calves. Ketonuria was conspicuously absent. Nitrogen excretion in the urine was low, but was increased about 100 per cent above non-diabetic levels. Urinary glucose excretion was also roughly proportional to the food intake, being moderately high after feeding and zero during fasting. As judged from the blood sugar curves following intravenous injections of glucose, 1 gm. per kgm. body weight, the glucose tolerance of these animals was definitely below determined preoperative levels, however, only 30 to 50 per cent of the administered sugar was excreted, some apparently being utilized. Although in apparently good physical condition, the animals slowly but progressively lost weight, digestive disturbances seemed to play an important rôle. They were sacrificed for terminal chemical analyses at 2 and 3 weeks postoperative. Muscle glycogen values were 0.52 and 0.77 per cent; liver glycogen values were 2.3 and 2.5 per cent in the two animals. The color of the livers was normal. The present results indicate relatively low levels of fat metabolism and endogenous gluconeogenesis in this species following pancreatectomy. These differences are probably related to anterior pituitary functions.

**Motor changes in monkeys with internal capsule lesions.** ELIZABETH J. COWGILL (by invitation) and H. W. MAGOUN. *Inst. of Neurology and Dept. of Anatomy, Northwestern Univ. Medical School, Chicago.* Electrolytic lesions were placed in the internal capsule of seven monkeys with the stereotaxic instrument. A lesion was designed which would interrupt all cortical fibers entering the internal capsule. Histological examination proves that the lesions were correctly placed.

Three animals were prepared with complete unilateral lesions. The resulting loss of voluntary movement on the contralateral side was most marked in the lower leg and least marked in the facial muscles. The loss of tone approached complete flaccidity post-operatively. Deep tendon reflexes were diminished to absent. Abdominal and plantar reflexes and placing and hopping reactions were absent. There was gradual return of voluntary control which was more rapid for gross movements and was never entirely complete for fine movements. There was no spasticity.

Two animals with lesions in anterior and two with lesions in the posterior limb of the capsule

<sup>1</sup> Work done under contracts with: (1) United States Army Air Forces, Wright Field, Dayton, Ohio, and (2) the Office of Scientific Research and Development, National Research Council, Washington, D. C.

demonstrated the same picture to a slightly less degree and showed more rapid recovery of voluntary control.

One animal in which a second complete lesion was produced, making it bilateral, exhibited marked rigidity and spasticity with very slow return of voluntary movement which was accompanied by a coarse tremor on effort. After six months, the monkey can walk fairly well without support.

**Autonomic function and electroencephalogram.** CHESTER W. DARROW, JULIAN H. PATHMAN (by invitation) and GISELA KRONENBERG (by invitation) *Inst. for Juvenile Research, Chicago.* Analysis of results from 120 persons, aged 7 to 40, with systolic blood pressure above 110, on whom our data for autonomic and electroencephalographic changes during hyperventilation are most complete, indicates significant relationships: Voltage of predominant sinusoidal, rhythmic (alpha?) activity above 6 per second gave correlations,  $r$ , of 0.28 with initial palmar skin conductance (sweating), of 0.33 with initial heart rate, and of 0.48 with combined conductance plus twice heart rate (empirically determined weighting). Independence of frequency is shown by correlations of 0.38, 0.30, and 0.43 respectively when frequency range is limited to  $10 \pm 1$  ( $N = 77$ ). Frequency gave correlations for the 120 cases of only -0.20, -0.21, -0.21, with these measures.

Since palmar sweating is sympathetically innervated, and since heart rate is accelerated by both sympathetic excitation and inhibition of parasympathetic tone (the latter most important), it appears that presence of sympathetic tone and limitation of parasympathetic tone relate to strong EEG potential. Correlations with combined measures suggest synergistic action. The present finding may be but another of the numerous conditions where physiological influences favorable to cerebral vasoconstriction also increase EEG potential at alpha frequency, and where those favoring vasodilatation decrease it. Concomitant effects of autonomic function on cell permeability are probably involved. That other physiological influences,  $\text{CO}_2$ , for example, contribute independently of autonomic impulses to these changes may well explain why still larger correlations are not obtained.

**Improvement of the electroencephalogram by atropine.** CHESTER W. DARROW, JULIAN H. PATHMAN (by invitation) and GISELA KRONENBERG (by invitation). *Inst. for Juvenile Research, Chicago.* Increase by atropine of high potential EEG waves in cats curarized with beta erythroiden (J. Neurophysiol. April 1944) caused us to anticipate similar effects in human cases. Finding of general improvement after atropine,  $\frac{1}{2}$  to  $\frac{1}{4}$  gr. by mouth, required explanation.

Analysis of simultaneous autonomic and EEG records of these patients shows that improvement, involving decrease of slow, random sharp, and low-potential fast spiky waves, tends to occur following atropine when heart rate is concomitantly slowed, and aggravation when it is increased. Most often, slowing of heart rate is accompanied by a rise in blood pressure, but sometimes by no change. In both conditions sensitization of moderator (carotid sinus?) mechanisms, either directly by the drug or secondarily by the rise of blood pressure, may be involved. In either case, increase of carotid sinus controlled parasympathetic, cholinergic impulses to the brain may be involved at the same time that there is a direct, though diffuse, anticholinergic (sedative?) action of atropine. When, as previously, high-potential slow waves are increased by hyperventilation after atropine, heart rate is most accelerated.

Differences from earlier observations are attributed largely to the absence of beta erythroiden.

**The renal clearance of carbonic anhydrase.** HORACE W. DAVENPORT. *Dept. of Physiology, Harvard Medical School, Boston.* Large amounts of laked erythrocytes were injected intravenously into anesthetized dogs previously given water and sodium bicarbonate by mouth and creatinine subcutaneously. Plasma and urine were analysed for hemoglobin, carbonic anhydrase and creatinine. Plasma carbonic anhydrase values were corrected for the presence of the specific protein inhibitor found in dog plasma.

Hemoglobin and carbonic anhydrase disappeared from the plasma at approximately the same rate. Less than 2% of the carbonic anhydrase appeared in the urine in  $2\frac{1}{2}$  hours. The ratio of hemoglobin clearance to creatinine clearance averaged 0.030 and was relatively independent of the plasma concentration. The ratio of carbonic anhydrase clearance to creatinine clearance was never greater than 0.038, and it decreased sharply with decreasing plasma concentration. The total plasma carbonic anhydrase concentration at which the clearance ratio was 0.01 was high when the plasma inhibitor content was high and low when the plasma inhibitor content was low. It is concluded that carbonic anhydrase (M.W. = 30,000) when free in the plasma can be filtered through a small percentage of the pores in the glomerular membrane, but the compound it forms with the protein inhibitor (M.W. > 68,000) cannot be filtered.

**Brilliant vital red and T-1824: Comparative studies.** PHILIP DOW. *Dcpt. of Physiology, Univ. Ga. School of Med., Augusta.* Brilliant Vital Red and T-1824 are acknowledged to be the only two dyes whose rate of disappearance from the circulation is sufficiently slow to permit their use for the calculation of intravascular dilution. However ever there appear to be numerous unreconciled

differences between results reported from the use of the two dyes, and data in the literature are too inconsistent to permit rigorous comparisons.

A firm linkage to plasma albumin has been shown to be closely related to the retention of these dyes in the blood. Some quantitative determinations of this linkage have been made in the case of T-1824 (Rawson, 1942). The current stage of this study applies similar spectrophotometric analyses to both dyes. Results so far are qualitatively similar to those of Gregersen (1937) and Rawson (1942) but with important quantitative differences, some of which may be related to salt concentration.

In practically salt-free solutions, the reactions of the two dyes to purified serum albumin are very much alike. There appears to be less difference between them than between water and saline solutions of either dye alone. In each case there are two distinct families of absorption curves, at lower and higher concentrations of protein, whose critical analysis is in progress.

Preliminary studies of the kinetics of the reaction between T-1824 and serum albumin indicate only that it is not a slow process. (Crystallized bovine serum albumin was generously supplied by the Armour Laboratories.)

**The relation of the pancreas to the regulation of the blood lipids.** LESTER R. DRAGSTEDT, J. GARRETT ALLEN and E. MARIE SMITH (by invitation). *Dept. of Surgery of the Univ. of Chicago.* The following experimental observations suggest that the pancreas is intimately concerned with the regulation of the blood lipids. Total pancreatectomy in dogs causes a decrease in the total blood lipids to about one half the normal level, confirming Chaikoff and Kaplan. Complete occlusion of the pancreatic ducts or partial pancreatectomy plus occlusion of the ducts to the pancreas remnant cause a decrease in the blood lipids, which occurs sooner and is even more marked than after total pancreatectomy. The oral administration of autoclaved pancreas or of fat-free alcohol extracts of pancreas (lipocaine) raises the low blood lipids of these dogs to nearly normal values. The oral administration of fresh raw pancreas raises the low blood lipids to higher than normal levels, i.e. produces hyperlipemia. The similar feeding of raw pancreas to normal dogs has no effect on the blood lipid concentration. Complete deviation of the pancreatic juice to the exterior by means of a fistula of the isolated duodenum does not cause a fall in the blood lipids. Removal of 90 to 95 per cent of the pancreas leaving the remnant in connection with a pancreatic duct produces a persistent hyperlipemia even if the diabetes is accurately controlled with insulin. The oral administration of autoclaved pancreas or of alcohol extracts of pancreas have no

effect on this hyperlipemia and the feeding of fresh raw pancreas raises the blood lipids still further.

**Effect of various ions on serum phosphatase activity during liver disease.** VICTOR A. DRILL and D. S. RIGGS (by invitation). *Dept. of Pharmacology, Yale Univ. School of Medicine and Lab. of the Fairfield State Hospital, New Haven and Newtown, Conn.* Alkaline serum phosphatase was determined by the method of Bodansky. In both normal subjects and patients with hepatic damage  $MgSO_4$  (0.01M) had a slight stimulating effect on serum phosphatase activity, whereas  $NaF$  (0.01M) was without any consistent effect.

Concentrations of  $NaCN$  from 0.0001M to 0.1M had some inhibitory effect on the serum phosphatase activity of 6 normal subjects, the inhibition averaging 1.4 units of phosphatase per 100 cc. of serum. In 19 patients with high serum phosphatase values (up to 23 units) due to liver damage, the addition of  $NaCN$  to the substrate inhibited most of the phosphatase activity. This inhibition was nearly maximal with 0.005M  $NaCN$ . With this cyanide concentration the phosphatase activity ranged between 0.78 and 4.64 units, and was not greatly decreased by increasing the cyanide concentration to 0.1M. With maximal inhibition by cyanide the high serum phosphatase values of patients with hepatic disease were reduced to the same range as that of control patients. This would suggest that the increase in serum phosphatase activity during liver damage is due mainly to an alkaline phosphatase that is inhibited by cyanide.

**Effects of hexyl resorcinol and alkali on diffusion of insulin through various membranes.** ROBERT L. DRIVER (introduced by J. R. Murlin). *Dept. of Vital Economics, School of Medicine and Dentistry, Univ. of Rochester, Rochester, N. Y.* A study has been made of the effect of hexyl resorcinol and alkali on the diffusion of insulin through the following membranes: sintered glass, mesenteric, egg, Cellophane and parchment paper. The amount of insulin diffused was calculated from nitrogen determinations.

Hexyl resorcinol had no appreciable effect on the rate of diffusion through a sintered glass membrane, but decreased it by 30% through mesenteric membranes, by 70% through egg membranes, by 30% through Cellophane and by 35% through parchment paper. Since hexyl resorcinol is a powerful surface tension lowering agent, and since it has been shown that surface tension is not a factor in the absorption of insulin from the intestinal tract, it was concluded that diffusion is not increased by a change in this physical property.

Alkali (sodium carbonate-bicarbonate buffer with a pH of 10) inhibited the diffusion of insulin through egg, Cellophane and parchment paper membranes but increased diffusion through fresh mesenteric membranes.

However, the diffusion of insulin through each of the four membranes was increased when it took place in the presence of both hexyl resoreinol and alkali.

The protective influence of mineral oil in experimentally produced ulcers. ROBERT L. DRIVER (introduced by Emmett B. Carmichael). *Dept. of Physiological Chemistry, Univ. of Alabama, School of Medicine.* In one group of experiments, loops of intestines of anesthetized dogs were subjected to a solution of 0.1% pepsin in N/HCl under a hydrostatic pressure of 90 cm. of water. Perforated ulcers appeared in an average time of 82 minutes. In another group of experiments the loops were treated the same way except that in this case the loops were exposed to heavy mineral oil before being subjected to the pepsin-HCl solution. The average time for perforated ulcers to occur was 130 minutes or an increase of about 60%. Considerable difference in the degree of damage was found in the two groups. In the loops not treated with mineral oil necrosis occurred over the entire area down to the serosa while in the treated loops damage was chiefly confined to the mucosa or muscle layers.

The experimental production of perforating ulcers with rennin in N/10 HCl. ROBERT L. DRIVER (introduced by Emmett B. Carmichael). *Dept. of Physiological Chemistry, Univ. of Alabama, School of Medicine.* It has been reported that the beneficial effect of milk in patients with ulcers of the alimentary tract may be due partly to the Ca content of the fluid (Driver, et al., *Science* 98: 158, 1943). The experiments described here suggest that milk may also exert its effect by reacting with rennin. Loops of intestines of anesthetized dogs exposed to N/10 HCl under a pressure of 90 cm. of water perforated in an average time of 174 minutes. If rennin was added to the HCl solution in a concentration of 0.1% the average time for perforations to appear was reduced to 114 minutes. These experiments led to the conclusion that pepsin is not the sole enzyme responsible for "peptic" ulcers.

The electrocardiogram of acute right ventricular ischemia produced by air embolism. THOMAS M. DURANT (by invitation), JOAN LONG (by invitation) and MORTON J. OPPENHEIMER. *Temple Univ. School of Medicine, Philadelphia, Penna.* Acute right ventricular dilatation and ischemia was produced in a series of dogs by the injection of air into the femoral vein. In the intact animal an injection of 25-50 cc. produced a mill-wheel murmur, a gallop rhythm, marked tachypnoea, a rise in venous pressure, and a very marked depression of the S-T segments in leads II and III of the electrocardiogram. Spontaneous recovery often occurred with rapid return to normal, and the same sequence of events could be repeated several times.

In open chest experiments with artificial anes-

thesia a similar injection was seen to produce sudden marked dilatation of right auricle and ventricle and the development of ischemia of the right ventricular outflow tract adjacent to the anterior descending branch of the left coronary artery. Air was found to be trapped in the pulmonary conus. Electrocardiographic leads from the area of ischemia showed, first, a sharp inversion of the T-waves, followed rapidly by a gradual, but marked rise in S-T segments obliterating the earlier T-wave changes. When recovery occurred there was a reversal of this sequence. Placing the animal on the left side was found to greatly favor recovery by displacing the air trap in the conus. The electrocardiographic changes were the same with the vagi intact or severed. There was no significant change in blood pH or carbon dioxide concentration. The changes are shown to be those of mechanically induced right ventricular ischemia.

The effect of breathing 100% oxygen on ventilation volume and alveolar CO<sub>2</sub> tension. A. EDELMANN (by invitation), W. V. WHITEHORN (by invitation) and F. A. HITCHCOCK. *Dept. of Physiology, Ohio State University, Columbus.*<sup>1</sup> The ventilation volume and alveolar CO<sub>2</sub> tension of normal male human subjects after breathing 100% oxygen for periods up to 90 minutes has been determined and the results compared to similar data obtained while the subjects were breathing outdoor air. The experimental procedure was as follows. The subjects (under basal conditions) lay on a comfortable bed for at least 15 minutes. Then, while breathing outdoor air, the ventilation volume was determined by collecting the expired air in a spirometer of the chain compensated type.

Collections of alveolar air were made. Both expiratory and inspiratory samples were taken each time. At the end of about 30 minutes (of breathing air) a valve was turned which connected the subject to a supply of 100% oxygen (Linde U.S.P.) and several (usually three) determinations of ventilation volume were made. Collections of alveolar air, as in the period of air breathing, were also made. All air samples were analyzed by means of the Haldane air analysis apparatus. With some of the subjects, control experiments were run in which the measurements made while breathing 100% oxygen preceded those made on outdoor air.

The results show that the ventilation volume while breathing oxygen is significantly greater (average about 20%) than while breathing outdoor air. The alveolar CO<sub>2</sub> tension was significantly lower on oxygen than on outdoor air. At present no explanation of the mechanism by which these changes are brought about can be made.

<sup>1</sup> The work described in this abstract was done under a contract recommended by the Committee on Medical Research, between the Office of Scientific Research and Development and the Ohio State University Research Foundation.

**Human vascular pole structures of the glomerulus and renal hypertension.** J. GRAHAM EDWARDS. *Dept. of Anatomy, School of Medicine, Univ. of Buffalo.* The vascular pole structures consisting of an epithelial plaque, a cluster of fibrocytes between the afferent and efferent arterioles and a hyperplastic wall of the afferent arteriole are believed by certain investigators to be causally related to the origin of renal hypertension. Secretory granules are claimed to be observable in the fibrocyte cluster and in the cells of the wall of the afferent arteriole. But no such granules are demonstrable normally or otherwise and certainly not in correlation with the production of renin, the precursor of hypertension.

In malignant hypertension, the fibrocyte cluster is frequently atrophic. Cellular changes in the cluster and in the wall of the afferent arteriole follow those in the interstitial tissue and renal arterial system, respectively. In interstitial nephritis cells of the cluster reflect closely that condition. Likewise, in proliferative or necrotizing arteritis or arteriolitis, the afferent arterioles are similarly affected as the renal arteries in general, especially those in the renal cortex. Thickened afferent arterioles lacking internal elastic membranes and described as normal in mammals generally, are not normal regardless of the mammals' state of health. The internal elastic membrane breaks down progressively as the afferent arteriole becomes hypertrophic, hyperplastic or degenerative.

The only renal structure suggestive of a causal relation to the origin or maintenance of renal hypertension as observed under a variety of conditions is the epithelial plaque, a unilateral modification of the tubule as it passes the vascular pole of the glomerulus.

**The effect of gold chloride on plasma ascorbic acid in the rat.** HERBERT ELITMAN and RAYMOND L. ZWEMER. *Dept. of Anatomy, College of Physicians and Surgeons, Columbia Univ.* Gold chloride was administered to a series of rats intraperitoneally in aqueous solution and the plasma ascorbic acid determined by the method of Farmer and Abt. In 7 rats receiving 9 doses of 15 mg. of gold per kg. in the course of two weeks, the plasma ascorbic acid dropped from an initial average of 1.07 mg. % to 0.36 mg. %. Two of the rats were kept for 3 additional weeks and given 5 additional doses of 15 mg. gold per kg., followed by 8 doses of 20 mg. gold per kg., resulting in final plasma ascorbic acid values of 0.13 and 0.28 mg. %. Similar results were obtained with lower dosages in rats and in a preliminary series of guinea pigs. The distribution of the gold in the tissues is being studied by histological methods. [funded by a grant from the Josiah Macy, Jr. Foundation.]

The effect of emotions on the occurrence of

pain. W. P. ELHARDT (introduced by W. E. Burge). *Physiology Dept., Univ. of Illinois, Urbana.* A war veteran kept a record of his emotional states and their effect on the occurrence of pain resulting from a gunshot wound of the shoulder and hand. He attempted to correlate the occurrence of pain with excitement, anger, despair, sorrow and worry. He obtained the excitement stimulus by going to athletic events; the sorrow stimulus by going to sad movies and reading depressing stories; he experienced anger at various times as a result of arguments and other aggravating incidents; worry stimulus he got by worrying over business transactions; and despair was experienced at irregular intervals from various causes. These records were kept over a period of four years, and they show that pain accompanied excitement 85% of the time; sorrow, 92% of the time; anger alone was accompanied by pain about 55% of the time; worrying about business transactions and other conditions produced pain 90% of the time. The most effective producer of pain was a combination of anger followed by despair. This condition showed a correlation of 100%. The response from anger and excitement would suggest the release of adrenalin, but the subcutaneous injection of adrenalin with a resultant rise in blood pressure of 32 mm. of Hg failed to produce any subsequent pain. The results of the accumulated data seem to show that emotions have a very pronounced effect on the occurrence of pain resulting from traumatic injury.

The efficiency of grade walking on the treadmill. LESTER ERICKSON (by invitation), ERNST SIMONSSON and ANCEL KEYS. *Laby. of Physiological Hygiene, Univ. of Minnesota, Minneapolis.* The respiratory metabolism of two normal men was measured before, during and after treadmill walking at speeds of 2.5, 3.0, 3.5 and 4.0 m.p.h. at each of grades zero, 5%, 7.5% and 10%. Dietary and environmental conditions were constant. Repeated measurements at 5 minute intervals in work agreed within  $\pm 3\%$  and similar constancy was obtained in replication of entire experiments on different days.

The efficiency of climbing was calculated from the excess cost of grade versus level walking. Maximum efficiency at all grades was obtained at 3.0 to 3.5 m.p.h. The highest efficiency was achieved on a 5% grade, reaching 40.3% in one man and 35.2% in another. The greatest variations in efficiency occurred at the conditions of optimum grade and rate. The natural frequency of steps was dependent on the speed and independent of the grade. Both pulse rate and oxygen debt increased in linear progression with the energy expenditure, whether the increase was obtained by variation of speed or of grades. The coefficients of correlation between energy expenditure and pulse was +0.972

( $t = 15.35$ ), and between energy expenditure and oxygen debt was +0.976 ( $t = 16.9$ ).

**Comparative anticonvulsant and hypnotic action of some barbituric acid derivatives.** G. M. EVERETT (by invitation) and R. K. RICHARDS. *Dept. of Pharmacology, Abbott Labs., North Chicago, Ill.* Standardization of a technique to determine the protective action of drugs against Metrazol convulsions has made possible a critical comparison of various barbituric acids for their hypnotic and anticonvulsant action in mice. Dimethylbarbituric acid (1) has no hypnotic or anticonvulsant action. However, trimethylbarbituric acid (2) shows remarkable anticonvulsant activity in mice and eats in doses which produce no sedation. The hypnotic dose is above 1 gm./kg. With 1-methyl-5-methyl-5-ethylbarbituric acid (3) hypnotic properties are more pronounced. Anticonvulsant action with non-sedative doses is somewhat less than (2). 1-methyl-5,5-diethylbarbituric acid (4) is a more powerful hypnotic than (3) but in non-sedative doses showed anticonvulsant activity equal to (2). Phenylcetylbarbituric acid is a powerful hypnotic and also an effective anticonvulsant in doses producing slight ataxia. 1-methyl-5-phenyl-5-ethylbarbituric acid has marked hypnotic properties but is an effective anticonvulsant only in doses producing ataxia. In contrast to these drugs is dicrotyl barbituric acid which is a central excitant but also an anticonvulsant.

Higher saturated aliphatic members such as pentobarbital and octylethylbarbituric acid show powerful hypnotic properties but relatively poor anticonvulsant activity even in doses causing sedation and ataxia.

**The renal reabsorption of amino acids in dogs. Histidine, arginine and lysine.<sup>1</sup>** FREDERICK P. FENGUSON (by invitation), FRANCES T. BYRN (by invitation) and A. G. EATON. *Dept. of Physiology, Louisiana State Univ. Medical Center, New Orleans 13.* The renal reabsorption of the three basic amino acids, arginine, histidine, and lysine, in unanesthetized female dogs has been studied by determining simultaneously the clearance of inulin or creatinine and that of the monohydrochloride of the particular acid under consideration. Plasma amino-nitrogen levels ranged between 5 and 40 mg. % and amino-nitrogen filtration rates between 5 and 40 mg./minute/sq. meter of body area. Of the acids studied, histidine is most rapidly reabsorbed. Increasing amounts are reabsorbed as the plasma level is raised, and there is little tendency to plateau at levels reached in our experiments. This is in accord with results obtained with glycine by Pitts (Am. J. Physiol. 140: 156, 1943) and by ourselves (unpublished observations). The reabsorption of arginine is much slower than that of

histidine at corresponding plasma levels, and there is an early tendency to plateau. While the results with lysine are somewhat erratic, its reabsorption is undoubtedly slow. The results with these three acids parallel those obtained by studies of the rates of absorption of the same acids from the intestine (Doty and Eaton, Am. J. Physiol. 123: 53, 1938) and suggest but by no means prove that the mechanism is the same in both cases. Both reabsorption by the kidney tubules and absorption from the intestine of these acids display a remarkable parallelism with the rates of deamination studied by Eaton and Doty (J. Nutrition 17: 497, 505, 1939; 21: 25, 1941).

**Seasonal variation in the threshold of the turtle's vagus nerve as shown by the activity of the heart and stomach.** DOROTHY FETTER. *Brooklyn College, Brooklyn, N. Y.* An alternating current was led through a rheostat and then through the electrodes with which the turtle's vagus nerve was stimulated. The amount of current from the rheostat was recorded by a voltmeter. Acute experiments were performed once a week from February 29th to August 17th. To stop the heart, the right vagus required a threshold of 0.4 to 0.5 volts during March, April, and May. From June through August the threshold was usually about one volt. (Extremes 0.75 to 1.5 volts.) The left vagus threshold during March and April was usually between 0.6 and 0.7 volts. From May through August the left vagus effect required 1.3 volts. (Extremes 0.8 to 3.5 volts.)

In most experiments the stomach went into activity at the same threshold which stopped the heart. The exceptional cases showed higher threshold values for stomach activity with the right vagus and lower for the left. The right vagus has a predominating effect on the turtle's heart and the left vagus predominates on the stomach. The heart threshold becomes high during the summer which seems adapted to the animal's activity, but the stomach threshold also becomes high which is not so adapted.

Previous experiments showed that potassium and strophanthin lowered the vagus threshold for the heart and raised it for the stomach (Howell, Am. J. Physiol. 15: 28, 1905; Fetter, Coombs, Pike, Am. J. Digest. Dis. 10: 303, 1943). Administration of these drugs intravenously or by stomach confirmed the above experiments. No variation occurred with the season.

**The response of respiratory and locomotor muscles to exogenous acetylcholine.** JOHN C. FINERTY (by invitation) and ROBERT GESELL. *Univ. of Michigan.* Contractions of the muscles of breathing (rectus abdominis, mylohyoid, and geniohyoid of the frog, mylohyoid of the turtle and diaphragm of the alligator) elicited by immersion in an acetylcholine containing Ringer's solu-

<sup>1</sup> Aided by a grant from the Rockefeller Foundation.

tion were potentiated by the addition of carbon dioxide. Contractions of muscles primarily locomotor in function (*sartorius*, *peroneus* and *gracilis* of the frog) were weakened. When, however, the carbon dioxide content of the external acetylcholine environment was increased but the pH was maintained at a constant value by proper additions of sodium bicarbonate and carbon dioxide to the Ringer's solution the contractions of both locomotor and respiratory muscles were potentiated. This potentiation of contractions of locomotor muscles is thought to be similar to that produced by carbon dioxide on respiratory muscles, for if carbon dioxide enters the muscle fiber more rapidly than bicarbonate (Jacobs) it should increase intracellular pH and delay hydrolysis of acetylcholine at the motor end plates and thus increase the intensity of humoral stimulation.

It is suggested that the prevention of potentiation of response of locomotor muscles to acetylcholine by carbon dioxide may be an evolutionary adaptation favoring a limitation of potentiation of contractions to the respiratory muscles proper during conditions of respiratory stress. The lesser sensitivity of the cord to asphyxia as compared with the medulla, noted by Mathison, and King, Garrey and Bryan, and others, may be regarded as another adaptation tending to prevent unnecessary locomotor activity immediately after the need of augmented muscular activity has ended. It is pointed out that cholinergic motivation of end organs and nerve cells shows evidence of being highly adapted to the variable requirements of the cholinergic system.

The influence of electrical daily stimulation upon the changes in muscle proteins during denervation atrophy. ERNST FISCHER and VIRGINIA W. RAMSEY (by invitation). *Baruch Center of Physical Medicine, Medical College of Virginia, Richmond.* In rabbits with both hind legs denervated, one *gastrocnemius* was tetanically stimulated vigorously with suitable electrical currents for short periods twice every day. After 14 days of treatment (15 days after denervation), the weight and the isometric strength of the treated muscles were in the average 12.5% higher than those of the untreated muscles. Since weight and strength were increased by the treatment to the same extent, no improvement in contractile power per gm. muscle occurred. The increase in protein content was slight (from 175 to 178 mg./gm. muscle), but the amount of the LiCl-soluble fraction was much more distinctly increased (from 50.8 to 60.2 mg.). The fraction of the protein content of the crude extracts which could be obtained as purified myosin was also distinctly increased for the treated muscle. All these changes in muscle proteins produced by the electrical treatment are in the opposite direction of the changes caused by atrophy.

However, with the exception of the purified myosin fraction obtainable per protein content of the crude extracts, treatment failed to re-establish normal protein condition. Myosin from treated muscle were not more spinnable into thread than those from untreated muscles; and birefringence of otherwise comparable threads were the same for threads from treated and untreated muscles.

**Changes in muscle proteins during denervation atrophy.** ERNST FISCHER. *Baruch Center of Physical Medicine, Medical College of Virginia, Richmond.* In rabbits with one hind leg denervated, the course of atrophy of the *gastrocnemius* muscle was investigated by determination of isometric strength, weight, water content, protein content, amount of LiCl-soluble protein and amount of purified myosin obtainable. The weight loss is rapid for the first 18 days, but changes then rather abruptly into a relatively slow one (muscle weight at 18th day 58% of original weight; at 75th day 42%). During the first (quick) phase of atrophy, the isometric strength elicited by appropriate direct electrical tetanic stimulation diminishes with the same rate as the weight, thus leaving the contractile power (strength per gm. muscle) unaltered. However, during the second (slow) phase of atrophy, the contractile power diminishes (to 46% on the 75th day). From the onset of atrophy, the protein content per gm. muscle declines at a constant rate (normal muscle 187 mg.; atrophied muscle at 75th day 104 mg.). This loss in total protein is mainly due to loss of the LiCl-soluble protein fraction, which diminishes from 83.6 mg. to 11.7 mg. at 75th day. With progressing atrophy, the fraction of the protein content of the crude extracts which could be obtained as purified myosin declines constantly (normal muscle 56.0%, 75th day of atrophy 42.6%). Thus the amount of myosin obtainable per gm. muscles diminishes during 75 days of atrophy from 47.5 mg. to 5.5 mg. However, the myosin from atrophied muscles is less spinnable into threads than myosin from normal muscle; and birefringence of otherwise comparable threads is distinctly less for those from atrophied muscles.

**Comparative effectiveness of extracts of intestinal mucosa in stimulating the external secretions of the pancreas and the liver.** M. H. F. FRIEDMAN and WM. J. SNAPE (by invitation). *Dept. of Physiology, Jefferson Medical College.* Extracts of mucosa of the hog's small intestine, prepared by different procedures, were tested for their power to excite the external secretion of the pancreas and the flow of liver bile. All assays performed on unanesthetized animals were conducted under basal conditions. The juice was collected by temporary fistulae. The results are summarized in the following table:

Site of fistula	Time of collection	Volume (ml.)	Specific gravity
pancreas	1 hr.	1.0	1.000
liver	1 hr.	1.0	1.000
cholecyst	1 hr.	1.0	1.000

the common bile duct. Each of the extracts was administered intravenously in standard doses.

No correlation was found between the secretin effects and the choleric effects of the extracts. While all potent secretin preparations also were effective in stimulating secretion by the liver, not all extracts which were effective on the liver were effective on the pancreas. It is suggested that at least two substances effecting the liver may be extracted from the mucosa of the small intestine: one stimulates the liver but is without influence on the pancreas while the other is probably intimately related to, if not identical with, secretin.

**Correlation between enzyme content and specific gravity of pancreatic juice.** M. H. F. FRIEDMAN and J. EARL THOMAS. *Dept. of Physiology, Jefferson Medical College, Philadelphia.* The specific gravity, lipolytic activity and tryptic activity of dog's pancreatic juice were determined. The pancreatic juice was obtained from five trained unanesthetized dogs by direct intubation of the pancreatic duct thru a fistula of the duodenum. Pancreatic secretion was elicited by intestinal administration of peptone, soap, and hydrochloric acid as well as by intravenous administration of secretin. Lipase and trypsin concentrations were determined photocolorimetrically on tributyrin and albumin substrates respectively. Prolipase was activated by the means of sorbitan oleate incorporated with the substrate and trypsinogen by means of enterokinase obtained from the dog's intestine. Peptone produced a secretion of high lipolytic and tryptic activity and specific gravity, hydrochloric acid and secretin gave a secretion of low enzymatic activity and specific gravity, while soap was intermediate in effect. The enzymatic activity of pancreatic juice was found to bear a definite and almost rectilinear relationship to the specific gravity. The degree of correlation between enzyme concentration and specific gravity was characteristic of each dog.

**The electrical activity of single optic nerve fibers in cats.** ROBERT GALAMBOS and KARL LOWY (by invitation). *Dept. of Psychology, Univ. of Rochester.* Thirteen cats were used in this study. They were immobilized by decerebration or Dial anesthesia. With Ringer-filled micropipets (3-5  $\mu$  opening) inserted into the optic nerve behind the eyeball, the electrical discharge of more than 75 fibers was isolated and recorded photographically from a cathode-ray tube-face. Light stimulation was supplied by a 150 watt bulb; intensity was controlled by Wratten neutral filters, color by Wratten color filters.

Most fibers studied showed spontaneous discharge in darkness. As regards response to white light, four fiber-types were identified. Over half reacted to both "on" and "off" of the stimulus by increased discharge. A lesser number showed in-

creased activity only during "on" although an after-discharge was sometimes observed. A few fibers stopped all activity within about one second after "on." Of these, some showed a brief, but definite, "off" discharge as well. Finally, an occasional fiber discharged only at "off" although its spontaneous activity, if present, was inhibited by "on." No fiber isolated exhibited specific color reactions.

These results confirm, in the main, the findings recently related by Granit (J. Physiol. 103: 103, 1944). They support his theory that the sensory impulses leaving the retina are the resultant of complex excitatory and inhibitory processes as yet not clearly understood.

**Effect of vitamin B complex on higher nervous activity.** W. HORSLEY GANTT and MAX WINTROBE (by invitation). *Pavlovian Laby., Phipps Psychiatric Clinic and Dept. Medicine, Johns Hopkins Univ.* Four dogs were subjected to diet deficient in one or more vitamins of the B group. These animals had previously been in the laboratory several years during which time they elaborated conditional reflexes to different auditory stimuli connected with faradie shock to foreleg. When the animals had had a 100% differentiation between two tones for some months they were given the deficient diet, which was exactly the same quantitatively and qualitatively as the control diet except the vitamins which had been given in capsules were omitted. After 4 to 15 days the animals showed disturbances in the conditional reflexes which became progressively worse; this disturbance consisted in failure to differentiate notwithstanding repeated practice. There was no observable behavioristic nor demonstrable neurologic changes (hopping, placing, tendon, or sexual reflexes) during the two month period of the deficiency. Return to the adequate diet restored the differentiation. At a subsequent period after several months of perfect differentiation the dogs were put on the same deficient diet and there was again an impairment of conditional reflex equilibrium which was restored to normal a second time when the animals were returned to the adequate diet. Noteworthy was the loss of equilibrium between the conditional reflexes without any other observable changes in behavior or blood. These experiments suggest the need of daily adequate amounts of at least some of the vitamin B group for optimal mental performance, the requirement for which may be in excess of the need for physical health and muscular work.

**The effect of desoxycorticosterone acetate on the heart weight of adrenalectomized rats.** JOSEPH H. GAST (introduced by James A. Greene). *Dept. of Biochemistry, Baylor Univ. College of Medicine, Houston, Texas.* Numerous papers in recent years have described the effects of overdosage with de-

soxycorticosterone in animals and humans. Much of this work either has been done on normal animals, or has followed the administration of enormously excessive doses, or has not included a careful evaluation of the diet.

The present study was undertaken to observe the effect on the heart weight of desoxycorticosterone acetate injections just slightly in excess of the maintenance requirement for adrenalectomized animals in a good state of alimentation.

Adrenalectomized male and female albino rats were maintained on a diet adequate in protein and vitamins but with variable known intakes of sodium and potassium. Desoxycorticosterone acetate was injected subcutaneously at different levels and the animals were killed at varying intervals during treatment. The hearts were weighed and compared with expected heart weights calculated from final body weights by the formula of Ryland (*J. Clin. Investigation* 17: 391, 1938).

The results obtained under these conditions indicate that the relation of actual heart weight to calculated values is dependent on the level of desoxycorticosterone administered and the sodium and potassium intake. Examination of the hearts show neither gross nor microscopic lesions such as appear in extreme potassium deficiency or with excessive overdosage of desoxycorticosterone.

These results bear out the clinical experience with desoxycorticosterone in Addison's disease and furnish experimental evidence of the importance of the relation of sodium and potassium intake to dosage level of desoxycorticosterone in treating adrenalectomized animals to prevent the possibility of cardiac enlargement.

**Adrenal medulla in water diuresis and water intoxication.** ROBERT GAUNT, MARGARET CORDSEN (by invitation) and MILDRED LILING (by invitation). *Dept. of Biology, Washington Square College of Arts and Science, New York Univ.* Adrenalectomy reduces the diuretic response to water and increases the susceptibility to water intoxication—a deficiency generally attributed exclusively to cortical ablation (Eversole, et al. '40). Stein and Wertheimer have, however, reported experiments on demedullated rats showing a diminished diuretic response to water and a "markedly enhanced susceptibility to water intoxication" and found that these effects were reparable by epinephrine injections.

We have extended earlier observations by methods of Gaunt (*Endocrinology* 31: 400, 1944) with following results:

I. In rats tested 3 or more weeks after bilateral demedullation, there was no deficiency in the excretion of 5 doses of water (25 tests), and normal susceptibility to the toxic effects of 13 doses (14 tests). In all respects normal and demedullated animals behaved alike.

2. Epinephrine injections (30 micrograms/100 gm. or more) increased diuresis both in normal and adrenalectomized animals, but gave little if any protection against toxic doses of water. (See also abstract by Hays and Mathieson in this journal.) The lack of definite protection against water intoxication was possibly associated with increased chloride excretion induced by epinephrine.

The pharmacological effects of injected epinephrine are clear in experiments of this type. The lack of corresponding deficiency phenomena in animals without adrenal medullae raises a question, however, as to the physiological significance of the medulla in the diuresis that follows water ingestion in normal animals, or in the lack of such diuresis following adrenalectomy. (Aided by a grant from the Josiah Macy, Jr. Foundation.)

**Water diuresis in pantothenic acid deficiency and its possible relation to adrenal function.** ROBERT GAUNT, MILDRED LILING (by invitation) and C. W. MUSHETT (by invitation). *Dept. of Biology, Washington Square College of Arts and Science, N. Y. Univ., and Merck Inst. for Therapeutic Research, Rahway, N. J.* Morphological evidence of adrenal cortical damage, but no conclusive evidence of impaired function, has been reported in pantothenic acid deficiency.

When adrenal function is depressed the diuretic response to water is subnormal and susceptibility to water intoxication is increased. Such responses to water are not seen in several other states of debilitation in which adrenal function is presumably normal (Gaunt et al., unpublished).

Accordingly water diuresis and intoxication tests were made in rats maintained on a purified diet presumably adequate in all respects, but lacking in pantothenic acid. The animals showed reduction in growth rate, coarse hair and achromotrichia. Controls were of three types: 1, pair-fed rats of the same age, fed a balanced purified diet; 2, animals of the same age fed *ad lib* the diet used in 1; 3, normal animals of the same size fed ordinary stock diet.

When 5 doses of water were given by stomach tube (methods of Gaunt, *Endocrinology* 34: 400, 1944) the pantothenic acid deficient animals showed a delayed diuresis, and when 13 doses were given a decreased resistance to water intoxication.

These deficiencies in handling water were completely relieved and resistance to water intoxication increased to normal by the administration of 3 mg. of desoxycorticosterone plus 1 or 2 cc. of adrenal cortical extract.

The abnormality in water metabolism of pantothenic acid deficient rats suggests that adrenal insufficiency may exist, but does not conclusively prove such a hypothesis. (Aided by a grant to R. G. from the Josiah Macy, Jr. Foundation.)

**Alveolar oxygen tensions and oxygen satura-**

*private ones of the writers and are not to be construed as official or reflecting the views of the Navy Department or the naval service at large.]*

Further studies on the preparation of extracts of marine oils capable of reducing the blood pressure of hypertensive animals. ARTHUR GROLLMAN. *Dept. of Experimental Medicine, The Southwestern Medical College, Dallas, Texas.* Earlier studies (Fed. Proc. 3:15, 1944) have demonstrated the capacity of various oxidized marine oils to lower the blood pressure of animals (rat, dog) rendered hypertensive by various manipulations on the kidney. It has been possible to obtain the active principle responsible for this action in an aqueous solution. This was accomplished by stirring the active oil with a suitable absorbant (amberlite), treating the resulting product repeatedly with a solvent (petroleum ether or skelly-solve) until the last traces of adhering oil are removed, and desorbing the active principle with diluted aqueous alkali. The resulting aqueous solution retains the blood pressure-reducing action of the original oil when administered orally to the hypertensive animal.

A toxic factor in ischemic compression shock.<sup>1</sup> HAROLD D. GREEN, GEORGES A. BERGERON (by invitation) and G. A. GUSTAFSON (by invitation). *Depts. of Physiology and Biochemistry, Western Reserve Univ. School of Medicine, Cleveland, O., and The Bowman Gray School of Medicine, Winston-Salem, N. C.* In a recent publication we postulated that the death with a shock like course which followed restoration of the circulation to the hind limbs of dogs after a 6 hour period of ischemic compression was due in part to release of a toxic factor (Am. Jour. Physiol. 142:494, 1944).

This has been tested by crosstransfusing 10 shock dogs with an equal number of test dogs (See Dennison and Green, Rev. Sci. Instruments—in press—for method). Since all the shock dogs died whereas all test dogs survived without even a temporary decline of arterial pressure it is concluded that no substance is released which is capable of inducing the shock state in an otherwise normal dog.

Since the urinary output falls shortly after release of compression in the shock dogs, a similar crosstransfusion was performed between 6 shock dogs and 6 dogs whose ureters had been ligated just before start of the crosstransfusion. This study was controlled by a similar crosstransfusion between 3 pairs of dogs all of whose ureters were ligated. All dogs of both series died but the test dogs of the former series all died sooner than the shortest survivor of the control group. It is concluded, therefore, that a toxic factor is present in the blood of the shock dogs which contributes to their death in the presence of renal failure.

The effect of ergotamine on the external and internal secretion of the pancreas. HARRY GREENGARD, C. D. COLLINS (by invitation) and A. C. IVY. *Dept. of Physiology, Northwestern Univ. Medical School, Chicago, Ill.* It has been observed by us that ergotamine and dihydroergotamine will markedly inhibit or abolish the response of the pancreas to secretin; the duration of the inhibition is an hour or more after the injection of one milligram of material. The inhibition is apparently specific for secretin, since ergotamine does not affect the secretory response of the pancreas to prostigmine or to epinine, hence it apparently does not act by causing a functional obstruction of the pancreatic ducts. In view of a report of a patient who evidenced clinical signs of pancreatic insufficiency after taking ergotamine over a period of years for the relief of migraine headaches, an attempt was made to duplicate such a condition in dogs by daily injections of ergotamine. Over a period of several months, these animals have developed no definite signs of deficiency of the external secretion. This may be due to the large factor of safety which operates in the external secretion of the pancreas, and also to the fact that when inhibition of secretion by ergotamine is not complete, the juice collected is rich in enzymes. However, some of the animals evidenced a moderate glycosuria after being given ergotamine for several weeks. Oral glucose tolerance tests indicate alterations in the directions of a lowered tolerance, increasing with the duration of ergotamine treatment. Hence ergotamine apparently inhibits both the external and internal secretory activity of the pancreas. The manner in which it does so is at present obscure.

The preparation and biological assay of a pancreozymin concentrate. HARRY GREENGARD and A. C. IVY. *Dept. of Physiology, Northwestern Univ. Medical School, Chicago.* We have previously reported (Science 99: 350-351, 1944) that in the separation of extracts of the intestinal mucosa, the pancreozymin activity is present in the fraction precipitated by aniline in the course of the procedure for the isolation of secretin. Traces of secretin, and a considerable amount of other material, may be removed from the aniline precipitate by two extractions with methyl alcohol containing 1 per cent of HCl. The residue from this treatment is a white powder, freely soluble in water, and contains no secretin, cholecystokinin, or vasodepressor substances. It is conveniently assayed by the following procedure:—a dog with the pancreatic duct cannulated is given repeated injections of secretin in a dosage adequate to elicit about 3 cc. of pancreatic juice in 15 minutes, and the collections from the first 4 injections are discarded. The responses to the fifth and sixth injections are divided into 3-minute fractions and kept for enzyme analysis, and on the seventh and eighth injections, the pancreozym-

<sup>1</sup> Supported by a grant from the Commonwealth Fund.

min is added to the secretin, the juice collected is similarly fractionated, and the enzyme content compared with that of the control samples. The unit of pancreozymin may be defined as the amount which will raise the enzyme content of the second 3-minute fraction to the level of the first. In the case of the concentrate described above, 5 milligrams of material has this effect. A comparison of this material with a sample sent by Dr. Raper, prepared by fractionation with bile-salts, reveals that the two products are of approximately equal potency, but that Raper's material contained detectable amounts of secretin.

The fractional response of the pancreas to "impure and pure secretin". HARRY GREENGARD, D. F. DUTRON (by invitation) and A. C. IVY. *Dept. of Physiology, Northwestern Univ. Medical School, Chicago, Ill.* When the dog's pancreas was stimulated to secrete by a single injection of a secretin concentrate (SI) or by pure secretin prepared by regeneration from the crystalline picrolonate, it was noted that the first and last portions of the secretion, particularly the former, were of apparently greater density than that which was elaborated when the secretory response was at its height. Determinations of the enzyme content of the juice collected at 2-3 minute intervals following a single stimulus revealed that these apparent density differences were related to the enzyme content, in that the first portion was high in enzymes, whereas the portion collected while the secretory rate was maximal was enzyme-poor. An immediate repetition of the secretin injection after a return of the pancreas to the basal rate resulted in a similar secretory response, with the enzyme content of each fraction at a lower level. When the injections were repeated several times, it was noted that the pattern of the response, with regard to the volume and enzyme content of each fraction, became quite constant. The type of response was similar for both SI and pure secretin, except that in the former case the enzyme content of each fraction of juice collected was higher, since SI contains both secretin and pancreozymin. When pure secretin is injected, the juice collected at the height of the stimulus is remarkably low in enzymes. These results are not obtained by a continuous injection of secretin at a constant rate; when this is done, the enzyme content remains constant after an initial stabilization, and varies inversely with the secretory rate. Apparently the pancreas possesses the property of prompt regeneration of its enzymes. This does not depend on the operation of the animal's intrinsic pancreozymin mechanism, as evidenced by the finding that in a dog with the entire intestinal tract removed, the fractional response of the pancreas to both SI and pure secretin presented no deviations from that in animals with the alimentary tract intact.

Comparison of plasma volume measured with the blue dye T-1824 and with beef albumin,<sup>1</sup> beef globulin<sup>1</sup> and the pneumococcus polysaccharide SIII<sup>2</sup>. M. I. GREGERSEN, A. A. BOYDEN (by invitation) and J. B. ALLISON (by invitation). *Dept. of Physiology, College of Physicians and Surgeons, Columbia Univ., and Dept. of Zoology, Rutgers-Univ.* The experiments were done on dogs. Measured amounts of dye and of one of the antigenic substances were injected simultaneously after being mixed in a syringe. Blood samples were drawn at 2½, 5, 10, 15, 20, 30, 45, 60, 90 and 120 minutes and the plasma volume calculated from extrapolation of the time-concentration curve (Gregersen and Rawson, 1943). The dye determinations were done on the serum with the Koenigs-Martens spectrophotometer. The antigenic substances were determined by the Libby Photronreflectometer with reference to a standard turbidity curve prepared with known antigen diluted in buffered saline containing the dogs' own serum.

The present summary is based on 7 experiments with beef albumin, 2 with beef globulin and 3 with SIII. The plasma volume measured with each of these agreed within experimental error with the values measured simultaneously with T-1824. The per cent differences ranged from +5.9 to -6.2 per cent. If all the results are averaged, the plasma volume measured with T-1824 is +0.05 per cent higher than that obtained with the antigenic substances.

Alkali therapy in acidosis.<sup>3</sup> E. M. GREISHEIMER, H. W. ROBINSON (by invitation), J. K. WESTON (by invitation), WALDO E. NELSON (by invitation) and M. J. OPPENHEIMER. *Temple Univ. School of Medicine, Philadelphia, Penna.* Twenty-five dogs have been brought into a critical state of acidosis by the oral administration of ammonium chloride. The course has been followed by determinations of serum carbon dioxide content, chloride, total base and pH.

Ten of the twenty-five dogs were treated with sodium bicarbonate. The amount of a 5% solution calculated to bring the body alkali reserve back to its normal value was injected intravenously. In most cases follow-up determinations were made at the end of an hour and also the following morning. Of these ten, seven survived and three died. Of the untreated group, six survived and nine died. When the dogs die or are sacrificed, serial sections of brain and spinal cord are made to ascertain if permanent changes occur. These findings will be

<sup>1</sup> Provided by Dr. Edwin Cohn, Harvard Medical School.

<sup>2</sup> Provided by Dr. M. Heidelberger, College of Physicians and Surgeons, Columbia University.

<sup>3</sup> This work was done under a contract, recommended by the Committee on Medical Research, between the Office of Scientific Research and Development and Columbia University.

<sup>1</sup> T-1824 was aide grant from the Merck Foundation.

reported later. In addition, the remainder of the tissues are subjected to pathological examination.

The average pH (38°) control value was 7.38; at the most critical phase it was 6.96. The CO<sub>2</sub> content fell from 56 to 20 vol. %. In spite of the very low pH values, the CO<sub>2</sub> content in our dogs (15 to 30 vol. %) did not reach the low level which is encountered often in human patients (2 to 10). With acidosis, the chloride rose from 106 to 120 mEq. and the total base fell from 161 to 153 mEq. (method of Polis and Reinhold using Amberlite-IR 100 furnished by Resinous Products and Chemical Company).

The study is being continued with other methods of therapy.

**Blood pressure response to changes of pressure on the spinal cord.** R. A. GROAT and T. L. PEELE (both introduced by W. F. Windle). *Inst. of Neurology, Northwestern Univ. Medical School, Chicago.* In cats in which the brain had been removed or functionally destroyed by asphyxiation or in which the dura and spinal cord had been ligatured in the cervical region, increased pressure on the portion of the cord which gives rise to the sympathetic outflow elicited a great rise in blood pressure. Liberation of pressor principles into the blood was not an essential factor in this response.

A maximum pressure of only 35 mm. Hg existed in the spinal intradural sac when intracranial pressure was raised to as high as 250 mm. Increased intracranial pressure in animals with the brain destroyed by asphyxiation elicited no pressor response, although increased spinal intradural pressure elicited great rise in blood pressure in these animals.

Pressor responses were compared in cats in which intracranial and spinal intradural pressures could be raised independently or simultaneously and in which vagi were sectioned and carotid sinuses denervated. Highest absolute blood pressure values occurred when intracranial and spinal intradural pressures were raised simultaneously. In general, increased spinal intradural pressure evoked elevation of blood pressure to absolute levels as high as or only slightly lower than those accompanying increased intracranial pressure. The blood pressure increment tended to be somewhat greater in increased spinal intradural pressure because of the lower initial blood pressure levels.

The portion of the central pressor mechanism located in the spinal cord is more resistant to prolonged asphyxia than is the portion located in the brain. [Work done under contract, sponsored by CMR, between OSRD and Northwestern Univ.]

**Relationship of speed of motor reaction to blood sugar level during acute starvation in man.** HAROLD GEETZKOW (by invitation), HENRY LONGSTREET TAYLOR, JOSEF BROZEK (by invitation) and ANCEL KEYS. *Laby. of Physiological*

*Hygiene, Univ. of Minnesota, Minneapolis.* Ten normal young men underwent a 2 day total fast, combined with 4 hours of walking on a treadmill at 3.5 mph, 10% grade. Total daily caloric expenditure was about 4,300 Calories. At the end of the 1st and 4th hour of work, 2 sets of 25 motor reactions to visual stimuli were measured. The reaction involved bending and striking selected telegraph keys while walking. After each set antecubital venous blood was drawn.

In general, speed of reaction changed parallel to blood sugar. Blood sugars in mg% on the first and second days were 71 and 52 for the 1st hour of work, 64 and 52 for the 4th hour of work; corresponding reaction speeds were 100, 91%, and 96.5, 92.6%. The coefficient of correlation between sugar and speed was 0.65 (40 pairs). The correlation was negligible when the sugar was more than 65 to 70 mg%. Reliability of sugar and speed measurements, in terms of the correlation between duplicate determinations, were 0.95 and 0.86 respectively.

In a similar experiment on 3 other men, the fasting period was extended to three and a half days. Sugar values at the end of the 1st hour of work were 71, 64, 54, 52 and the 4th hour, 63, 60, 60. Corresponding speeds of voluntary motor reaction were 100, 94.2, 94.6, 97.2% and 98.8, 96.3, 96.8%. The coefficient of correlation was 0.56 (21 pairs). Other psychomotor test performances involving speed showed similar relations to the blood sugar. [This work was supported in part under the terms of a contract between the regents of the University of Minnesota and the Office of Scientific Research and Development. Support from other sources will be acknowledged in final publication.]

**The effects of various sulfonamide drugs on the electrocardiogram of the dog.**<sup>1</sup> ROBERTA HAFKES-BRING and GRACE E. WERTENBERGER. *Dept. of Physiology, Woman's Medical College of Pennsylvania, Philadelphia.* Several papers have appeared dealing with the histopathological effects of the sulfonamide drugs on cardiac muscle, but very few have dealt with the physiological effects.

In a previous electrocardiographic study on 16 dogs treated with the sodium salts of sulfapyridine, sulfathiazole and sulfadiazine, we found no significant changes in the electrocardiogram.

These studies have been continued and extended to include the sodium salts of sulfapyrazine and sulfamerazine. The present series was distributed as follows: sodium sulfapyridine (2 dogs), sodium sulfathiazole (2 dogs), sodium sulfadiazine (3 dogs), sodium sulfapyrazine (7 dogs) and sodium sulfamerazine (7 dogs), making a total of 21 animals.

After a control period of 3 weeks, the drug was

<sup>1</sup> Aided by a grant from the Committee on Therapeutic Research, Council on Pharmacy and Chemistry, American Medical Association.

administered by intraperitoneal injection on four consecutive days in divided doses totalling .65 gm./Kg for the period. The electrocardiogram (Lead 2) was recorded and the blood concentration of the drug determined four hours after each dose. A rest interval of 8-10 days was allowed between each drug period. Four series (total 16 doses) were run on each animal. The electrocardiogram was analyzed for heart rate and conduction time (P-R interval) and carefully checked for any abnormalities.

The blood level of the drug was always above the recommended therapeutic level, and most of the animals showed toxic effects. No significant change occurred in the electrocardiogram with the sulfonamides studied. Even in one dog with defective conduction (prolonged P-R interval with occasional dropped beats) the drug (sodium sulfamerazine) did not aggravate the condition and increase the defect.

**Comparative observations on the blood sugar level in normal young adults following meals containing high and low percentages of carbohydrate.** JOHN HALDI and WINFREY WYNN (by invitation). *Dept. of Physiology, Emory Univ., Emory, Ga.* It has been suggested that functional hypoglycemia, which appears to be a well established clinical entity, may be a fairly common occurrence and responsible for feelings of tiredness, weakness and hunger in mid-morning or mid-afternoon. This condition has been attributed to relatively large amounts of carbohydrate in the diet. From a dietary hygienic point of view it is important to know whether this assumption has a factual basis.

Fifty nine medical students ate a breakfast which contained 385 calories with 81.5% of the total energy derived from carbohydrate, for four consecutive mornings. Blood samples were taken for sugar determinations two and one-half to three hours later. The procedure was then repeated with an isoenergetic meal supplying 26.6% of the calories from carbohydrate. The average blood sugar level was 101 mgm. percent after the low carbohydrate meal and 99 mgm. percent following the high carbohydrate breakfast. There were no values below 80.

In another experiment twelve swimmers were given a thousand caloric meal providing an alternate day 73.5% and 22.5% of the energy from carbohydrate. Approximately three hours after eating they swam a hundred yard sprint. On each occasion they exerted themselves to the utmost. There was no significant difference in the blood sugar nor in the performance on the two types of meals.

These data are considered sufficient to show that in normal individuals a high carbohydrate meal does not lead to hypoglycemia two or three hours later nor to a lessened capacity for strenuous work of short duration.

**Physiological adjustments to altitude.** F. G.

HALL, LT. COL., A.C. *Aero Medical Laby., Wright Field.* Physiological adjustment to high altitude appears to fall into three fairly distinct categories—accommodation, acclimatization, and adaptation. Accommodation is the first physiological response to changes in barometric pressure. It was found that pulmonary ventilation is the same for a given degree of activity from ground level to barometric pressures equivalent to 35,000 feet altitude. Above this altitude pulmonary ventilation increases; the degree of the increase dependent upon the level of activity. The ratio of maximal inspiratory flow to pulmonary ventilation is higher with resting than with an exercising individual. There are no changes in hemoglobin concentration with rapid changes in barometric pressure or with short exposures to low barometric pressures. Acclimatization follows prolonged exposures to low barometric pressures. Acclimatization may be manifest as low as 5000 feet altitude as illustrated by changes in composition of respiratory gases and hemoglobin concentration. There are numerous physiological adaptations to low barometric pressures such as high oxygen combining power of hemoglobin. This involves study in comparative physiology since adaptations are fixed by heredity and are unchanged in the individual. Survival of animals to changes in barometric pressure depends upon the extent to which these physiological adjustments can be brought into play.

**The human centrifuge. Demonstration (motion picture).** F. G. HALL, GEORGE L. MAISON, G. A. HALLENBECK (by invitation) and C. A. MAASKE (by invitation). *Physiological Branch, Aero Medical Laby., Engineering Division, AAF Air Technical Service Command, Wright Field, O.* A motion picture with sound track illustrating the construction and use of the AAF Air Technical Service Command centrifuge. The turn table is 48 feet in length, bearing a cab for human occupancy at each end. One cab is adapted for the prone subject, the other for the seated subject. The drive mechanism is photoelectrically controlled and entirely electrically operated. Braking is dynamie.

The machine in its present form will take a live load of 400 pounds with a factor of safety of three to a maximum centrifugal force of 20 times normal gravity. Linear speed at the cab station at 20 "g" is approximately 90 miles per hour. The accelerating mechanism is capable of translating the cab from standstill to this speed in approximately 10 seconds.

The motion picture traces the course of a typical subject through a series of rides on the centrifuge, shows the recording mechanisms available and the face of the subject while undergoing the force.

**Effects on man of repetitive exposure to centrifugal force.** G. A. HALLENBECK (introduced by F. G. Hall). *Physiological Branch, Aero Medical*

Laby., Engineering Division, AAF Air Technical Service Command, Wright Field, O. This study was undertaken to determine the response of subjects to increased "g" when exposures follow one another at time intervals brief enough that the response to one exposure could be conditioned by previous trials. The Air Technical Service Command centrifuge was operated such that six ten-second episodes of 4.2 "g", a level sufficient to produce marked visual symptoms in the chosen subjects in a single test run, were delivered in sequence. Time intervals from the end of maximal "g" in one episode to the beginning of maximal "g" in the next were set at 4.7, 9.6, 19.4 and 29.1 seconds. Continuous exposure for 60 seconds was also imposed. During continuous 60 second exposures, six subjects who suffered either loss of peripheral vision or blackout during the first ten or fifteen seconds showed varying degrees of improvement in vision thereafter. When exposed to the series of repeated ten second episodes of increased "g", the six subjects showed improvement of vision in the second and subsequent episodes of each series. This improvement was constant and marked when the interval between exposures was ten seconds or less, and less consistent when the interval was 15 or 30 seconds.

The principle of blended samples in validating behavioral indicators. WARD C. HALSTEAD. *Dept. of Medicine, Univ. of Chicago.* In developing behavioral indicators for brain damage in man, the problem of satisfactory control groups becomes extremely complicated. Industrial and automobile accidents, falls, acute or chronic illness, developmental anomalies, brain tumors, and accidents in certain sports are some of the factors which may produce sub-clinical brain injury in a large number of the so-called "normal" population. Random sampling which inadvertently includes such individuals thus contaminates a control group with the factor to be isolated. By the use of blended samples, systematic groups or clusters of such variables as age, sex, I.Q., education, occupation, *et cetera*, become the reference point of "normality." By selecting antithetical clusters, with the aid of charts prepared for this purpose, small and relatively "pure" control groups may be rapidly established. The principle is also applicable to experimental groups for studies such as localization of function in the brain.

Chronic intermittent anoxia and the dynamic visual field.<sup>1</sup> WARD C. HALSTEAD. *Dept. of Medicine, Univ. of Chicago.* Twenty male subjects, selected to meet the age, physical and mental standards of the Service Air Corps, were exposed

individually or in groups in a decompression chamber at a simulated altitude of 10,000 feet for 5 or 6 hours per day, 6 days per week, for 4 to 6 weeks. Control studies were made before and after the total period at altitude. Thirteen (65%) of these men developed a marked impairment of the dynamic visual field during the third or fourth week at altitude, which was reflected by an inability to perceive peripheral targets which had previously been readily detected. Once developed, the impairment could not be relieved at once by the inhalation of 100% O<sub>2</sub>. In some instances days or weeks were required for complete recovery after exposure. Fractional O<sub>2</sub> therapy prevented the impairment in one re-exposed subject in whom it had developed at initial exposure. The effect appeared earlier, was more marked and lasted longer in subjects exposed above 10,000 feet. These results indicate that former Service regulations requiring use of O<sub>2</sub> equipment on daylight missions above 10,000 feet did not provide an adequate margin of safety against the possible insidious effect of chronic intermittent low-grade anoxia.

**Localization of neuropsychological functions in the prefrontal lobes.** WARD C. HALSTEAD. *The Otho S. A. Sprague Memorial Institute and The Dept. of Medicine, Univ. of Chicago.* During the past ten years, a group of 22 neuropsychological indicators has been developed in this laboratory for quantitative analysis of the effects of brain injuries in man. Carefully selected neurosurgical, psychiatric, and other types of patients and normal individuals have been studied in detail by these methods. A deterioration index (impairment of neuropsychological functions) has been developed on the basis of performance on certain of the indicators while the others serve as a check on such factors as motivation, cooperation, and predominate personality trends. The average range in deterioration index for various groups studied is shown in Table 1 below.

TABLE 1

	Range of deterioration index	
	From	To
Control group.....	0.0	0.0
Psychoneurotics.....	0.2	0.3
Severe depressions.....	0.3	0.4
Occipital lobectomies.....	0.1	0.2
Parietal lobectomies.....	0.2	0.3
Temporal lobectomies.....	0.2	0.3
Unilateral prefrontal lobectomies.....	0.6	0.8
Closed head injuries.....	0.6	0.8
Bilateral prefrontal lobectomies.....	1.0	1.0
High grade anoxias.....	1.0	1.0

These results indicate localization in the prefrontal lobes of the functions tested in the sense of a region of peak effect. From analysis of the per-

<sup>1</sup> The work described in this abstract was done under a contract, recommended by the Committee on Medical Research, between the Office Scientific Research and Development and the University of Chicago. The initial findings were reported on October 1, 1942.

formances of a further group of patients before and after prefrontal lobotomy (an operation in which extensive sub-cortical damage is produced in both prefrontal lobes with relatively little damage to the cortex) it has proved possible to trace the localization farther to the cortex of the prefrontal lobes. These traditionally "silent" areas of the brain thus become of great importance in our understanding of the biological basis of intelligence:

**Relation between the volume-pressure curves of the aorta and the pulse wave velocity.** W. F. HAMILTON, JOHN W. REMINGTON and PHILIP Dow. *Dept. of physiology, Univ. of Georgia School of Med., Augusta.* The physical characteristics of rubber tubes and of aortae make it difficult to apply the classical equations relating pulse wave velocity to distensibility. The viscosity of the walls of the tube make it effectively less distensible when stretched rapidly than when stretched slowly. The relations shown on slow stretch indicate the systolic up take and the relations on rapid stretch, the pulse wave velocity. The uptake is 15-25% greater than the figure indicated by pulse wave velocity. Successive rapidly applied stretches cause the distensibility to approach that shown on slow stretching with unpredictable changes in absolute volume. The standing wave is therefore related to a pulse wave velocity that is slower than that of the transmission of the start of the pulse wave. Since the aorta is slow to resume its original volume after stretching (hysteresis), diastolic size of the aorta at any given diastolic pressure increases with greater pulse rates. So also does the pulse wave velocity but these changes are hard to relate to aortic uptake during systole.

**Somatotopic localization in anterior lobe and lobulus simplex of cerebellum in cat and dog.** JOHN L. HAMPTON (by invitation), CLINTON R. HARRISON (by invitation) and CLINTON N. WOOLSEY. *Dept. of Physiology, Johns Hopkins Univ., School of Medicine, Baltimore 5, Md.* Liminal faradic excitation of the cerebellar cortex reveals somatotopic localization in the anterior lobe and lobulus simplex of decerebrate animals and elicits from medial and lateral portions of the anterior lobe differential responses.

Main effects of brief stimulation (less than 1 sec.) of the medial  $\frac{1}{2}$  of the anterior lobe are: 1) active ipsilateral flexion and (or) incomplete ipsilateral extensor inhibition, 2) increased contralateral extension. Similar stimulation of the lateral  $\frac{1}{2}$  gives: 1) active ipsilateral extension, 2) rebound ipsilateral flexion.

Prolonged stimulation (15 sec.) of the medial  $\frac{1}{2}$  causes: 1) profound ipsilateral extensor inhibition, 2) strong contralateral extension, 3) marked rebound ipsilateral extension, 4) poststimulatory continuation of augmented contralateral extension. Similar excitation of the lateral  $\frac{1}{2}$  produces: 1)

initial active ipsilateral extension, reversing to 2) ipsilateral extensor inhibition, 3) strong rebound ipsilateral flexion.

Both types of stimulation disclose clearcut somatotopic localization as follows: neck in lobulus simplex, forelimbs in culmen, hindlimbs in lobulus centralis. Tail is most readily influenced from the lowest folia of centralis. Stimulation on either side of the fissure separating culmen and centralis causes simultaneous effects in fore- and hindlimbs and in trunk musculature.

The somatotopic sequence is essentially the same as that of the motor cortex. It agrees with the sensory sequence in the anterior lobe and lobulus simplex described by Snider and Stowell (1942, 1944) and by Adrian (1943). It is opposite to that defined by Connor (1941) with regional ablations.

**Reflex response to homolateral and bilateral faradic stimulation of Hering's nerve.** ELWOOD T. HANSEN (by invitation) and ROBERT GESELL. *Univ. of Michigan.* Weak stimulation of Hering's nerve reduces inspiratory and expiratory contractions. This inhibition increases with increasing strength of stimulation which may terminate in apnea. With mounting stimulation inspiratory contractions reappear first and augment progressively. Active expiratory contractions appear later and increase along with the inspiratory contractions.

When the current is weak the combined inhibitory response to stimulation of the left and right nerves is additive. This indicates a central summation of inhibition, presumably originating in sinus afferents.

The lengthening of a muscle in a coupled spinal reflex varies directly as the shortening of its antagonist (Sherrington). But since inhibition of both inspiratory and expiratory muscles in our experiments are associated with simultaneous weakening of contractions of their respective antagonists, the inhibition produced by stimulation of Hering's nerve is regarded as a direct reflex and not a reciprocal inhibition. It would, however, be unjustified to infer that direct inhibition is a common physiological occurrence, e.g., when a contralateral flexion reflex is inhibited by a homolateral reflex this inhibition is associated with coupled activity and may therefore be entirely reciprocal in nature.

With stronger stimulation the response is additive in the inspiratory and expiratory half-centers indicating that chemoreceptor afferents stimulate both half-centers. Acetylcholine accumulating at both half-centers results in what might be termed a "simultaneous summation" of coupled half-centers.

With vagi intact effects of combined stimulation are greater than expected simple direct summation. This "super summation" may be due to accessory

excitatory reflexes originating in the vagal proprioceptive endings.

**Changes in plasma modifying the release of pituitrin.** KENDRICK HARE, ELEANOR V. MELVILLE (by invitation), GEORGE H. CHAMBERS (by invitation) and RUTH S. HARE (by invitation). *Dept. of Physiology, State Univ. of Iowa, Iowa City.* It has been demonstrated that hypertonic saline infusions cause the release of pituitrin in the dog. The release of pituitrin in response to intravenous infusions of saline and other solutions has been investigated here by four methods: (1) assay of blood and urine collected before and after the infusion; (2) comparison of the response to the infusion with and without added pituitrin; (3) restoration of the response of a dog with diabetes insipidus to normal by graded doses of pituitrin; (4) effect of the infusion or injection of the solution on a pre-existing water diuresis. Solutions used include 3.9% sodium sulfate, 6.3% and 18.9% urea and 0.5 to 3.0% sodium chloride. Plasma was analysed for sodium, chloride and urea. Apparently the significant factor in the release of pituitrin is the change in osmotic pressure of the plasma, rather than the change in concentration of any of the particular substances studied.

**The life duration of the erythrocyte of the monkey (*Macacus rhesus*).** O. G. HARNE, JOHN F. LUTZ (by invitation), GRACE I. ZIMMERMAN (by invitation) and CARL L. DAVIS (by invitation). *Dept. of Histology, Univ. of Maryland School of Medicine, Baltimore.* The life duration of the erythrocyte of the monkey was studied by autonomous blood replacement following hemorrhage. Predetermined amounts of blood were withdrawn from the veins, following which daily reticulocyte counts were made to determine 1, the degree of replacement of erythrocytes during the initial reaction, and 2, the pattern of replacement in the course of adjustment following blood loss.

Two control and 10 experimental animals of both sexes, 6 to 8 years of age were used.

The reaction to hemorrhage may be divided into three phases, initial, interval, and spontaneous.

The initial reaction began 3 to 5 days after the hemorrhage, and lasted from 20 to 40 days in seven out of ten animals. In three animals the reactions were indefinite.

The reticulocyte output rose during the initial period to 321% above control level.

No fluctuations were observed in the erythrocyte output in the controls.

Following the initial reaction, the erythrocyte output returned to control level or below. This interval period lasted roughly another 40 days, when the reaction entered a (final or) spontaneous phase marked by a prolonged reticulocytosis. In every case (except the three mentioned above) this spontaneous reaction was extensive and produced

a marked elevation on the curve. We interpret this rise as a reaction of the hematopoietic organs to the mass disappearance or withdrawal of the erythrocytes thrown into the circulation immediately following the hemorrhage.

The time lapse, therefore, between the peaks of the initial and spontaneous reactions (97-117 days) expresses the life duration of the erythrocyte in the monkey.

**Bicarbonate and chloride of pancreatic juice in response to various stimuli.** W. M. HART (by invitation) and J. E. THOMAS. *Dept. of Physiology, Jefferson Medical College, Philadelphia.* Pancreatic juice was collected from unanesthetized dogs which had permanent tubulated fistulas of the stomach and duodenum. The duodenal fistula was opposite the main pancreatic duct. Pancreatic juice was collected through a temporary cannula inserted into the duct by way of the duodenal fistula as suggested by Scott (A. J. P. 134: 208, 1941). Five to twenty cc samples were collected without contact with air into a glass syringe connected with the cannula through a rubber tube. Otherwise the animals retained all their digestive secretions. Solutions of HCl, glutamic acid, peptone or soap were injected into the upper intestine to elicit a flow of pancreatic juice. In a few experiments secretin was given intravenously.

Total carbon dioxide was determined by a manometric method. A glass electrode with a closed cell was used for pH determinations at approximately 25 degrees. Previous observations of a reciprocal relation between bicarbonate concentration and concentration of chloride were confirmed; also the direct relation between bicarbonate concentration and rate of secretion, provided the rates were below 0.05 ml of juice per minute per Kilo body weight. At higher rates the bicarbonate concentration was independent of the rate of secretion and attained a constant maximum, characteristic of the animal. Maxima ranged between 135 and 148 mM/L.

No consistent relation was found between the concentration of inorganic constituents and either the stimulus used to promote secretion, or the total nitrogen content of the juice.

**Effect of desoxycorticosterone acetate and epinephrine on water diuresis in normal and adrenalectomized rats.** HARRY W. HAYS and DONALD R. MATHIESON (introduced by W. W. Swingle). *Dept. of Pharmacology, Ciba Pharmaceutical Products, Inc., Summit, N. J.* In all experiments, water was given by mouth according to the formula: Body Surface x 4 per cent x 4 hourly injections, and the percentage excretion determined at the end of seven hours. Normal rats excreted 83 per cent while rats adrenalectomized one day excreted only 20 per cent. When similar adrenalectomized rats were treated with doses of desoxycorticosterone acetate (D.C.A.)

ranging from 0.20 mg. to 3.0 mg. in oil the percentage exertion was directly proportional to the dose but seldom reached the same level as that of normal animals. At the same time there was a marked protection against death from water intoxication as evidenced by the fact that the 63 per cent mortality observed in the untreated adrenalectomized controls decreased to approximately 10 per cent in the treated group.

Adrenalectomized rats maintained on 1.0 mg. of D.C.A. per day for seven days and given water on the eighth day, excreted 17 per cent. When an additional 2.0 or 9.0 mg. was given on the seventh day, the percentage exertion was not increased. Control adrenalectomized rats maintained on physiologic sodium chloride solution for seven days, excreted 22 per cent of the water in seven hours. While the response to water diuresis was not increased in this experiment with daily hormone treatment, there was again a definite protection against death from water intoxication.

Rats receiving 0.15 mg. of epinephrine per 100 grams of body weight subcutaneously 18 hours after adrenalectomy and one-half hour before water was administered, excreted 63 per cent, while those receiving the same dose of epinephrine plus 3 mg. of D.C.A. excreted 78 per cent.

When adrenalectomized rats were maintained on 1.0 mg. of D.C.A. per day for seven days, the exertion at the end of seven hours was 17 per cent, while similarly treated animals receiving 0.15 mg. of epinephrine per 100 grams, excreted 79 per cent. Control adrenalectomized rats maintained on physiological salt solution for seven days excreted 22 per cent but when given 0.15 mg. of epinephrine per 100 grams the exertion increased to 50 per cent.

It would seem therefore that D.C.A. affords not only a protection against water intoxication but acts as a mild diuretic. When given D.C.A. in combination with epinephrine, adrenalectomized rats eliminate water as well as normal animals.

**Physiological changes during motion sickness.**  
**ALLAN HEMINGWAY**, Major, Air Corps. AAF  
*School of Aviation Medicine, Randolph Field, Texas.* Motion sickness was produced in normal young men by means of a twenty minute swing test. Blood pressures, pulse rates, body and skin temperatures and the rate of sweating was measured. It has been found that motion sickness is not associated with any significant change in systolic pressure, diastolic pressure or pulse rate. Cold sweating occurs during motion sickness with a drop in skin and mouth temperature and can occur in environments with air temperature near freezing. Hyperventilation frequently occurs causing tingling sensations in the feet and hands and occasionally carpo-pedal spasm. In a few instances this has been so severe that the hands have been

"frozen" to the supports and the fingers had to be pried loose. X-ray examination after a barium meal has shown a loss of gastric tonus and delayed emptying of the stomach as a result of motion sickness.

#### Blood lactate and pyruvate relations in man.

**AUSTIN HENSCHEL**, **HENRY LONGSTREET TAYLOR**, **OLAF MICKELSEN** (by invitation) and **ANCEL KEYS**. *Laby. of Physiological Hygiene, Univ. of Minnesota, Minneapolis.* Blood lactate and pyruvate concentration and the lactate-pyruvate ratio (L/P) was determined in young men at (1) basal rest, (2) 5 minutes after a 1 hour walk at 3½ miles per hour on a 10% grade, (3) 12 and 30 minutes after 90 seconds of "anaerobic" work (9 miles per hour, 10% grade), and (4) 60 minutes after the ingestion of 10<sub>s</sub> grams of glucose. The lactate and pyruvate concentrations, in mg. per 100 ml., and L/P were, respectively; (1) in basal rest, 6.5± 2.35, 0.95 0.293, 6.9± 1.81, (2) 5 minutes after aerobic work, 7.0± 1.38, 0.85± 0.191, 8.5± 1.68, (3) 12 minutes after "anaerobic" work, 75.8± 19.1, 3.49± 0.699, 21.9± 3.58, (4) 30 minutes after "anaerobic" work, 44.5± 15.1, 2.64± 0.552, 16.6± 3.32, (5) 60 minutes after 100 grams of glucose, 9.5± 3.50, 1.18± 0.339, 8.3± 2.52. In mild thiamine deficiency the lactate and pyruvate were slightly increased in basal rest and after aerobic and "anaerobic" work without any change in L/P. Blood lactate and pyruvate levels are of little value in clinical diagnosis of mild thiamine deficiency. During acute thiamine deficiency a significant increase in lactate and pyruvate with a decrease in L/P was especially marked in the subjects who had for months previously been on a borderline thiamine intake. The lactate, pyruvate and L/P were significantly increased by the ingestion of 100 grams of glucose even in subjects on ample thiamine intakes. [This work was supported in part under the terms of a contract between the Regents of the University of Minnesota and the Office of Scientific Research and Development. Support from other sources will be acknowledged in final publication.]

**Pyruvic acid cycle.** **HAROLD E. HIMWICH**, **EDMUND HOMBERGER** (by invitation) and **WILLIAMINA A. HIMWICH** (by invitation). *Dept. of Physiology and Pharmacology, Albany Medical College, Union Univ., Albany, N. Y.* Normal dogs, fasted 24 hours and under light nembutal anesthesia, were studied in a preliminary investigation of the pyruvic acid cycle. Blood was drawn from the femoral artery, femoral, hepatic and portal veins and from the cerebral longitudinal sinus, practically simultaneously. Three series of blood samples were collected, a control, another glucose and a third after insulin. The blood samples were analyzed for lactic acid, pyruvic acid, and glucose. The results for pyruvic acid are tabulated, ± indicating liberation, 0 no significant change, and —

absorption. A difference of more than 0.12 mg. per cent was considered significant.

	Control series			Glucose series			Insulin series		
	+	0	-	+	0	-	+	0	-
Liver.....	1	4	6	1	0	3	2	1	7
Muscle.....	3	3	5	0	0	4	4	3	2
Intestine.....	4	4	1	3	1	0	4	1	3
Brain.....	4	2	0	1	0	0	5	0	3

In the majority of instances the liver removed pyruvate from the blood stream while the other organs added it.

Observations on pressure relationships between the proximal and distal colon of dogs. JUSTIN HOEKSTRA (by invitation), F. R. STEGGERDA and A. B. TAYLOR (by invitation). *Dept. of Physiology, Univ. of Illinois, Urbana.* True intraluminal pressures were recorded in the proximal and distal colon, following the administration of various quantities of gas. Simultaneously, radiographs were made from previously visualized colons.

Rubber catheters, fitted with open metal tips, were introduced into the proximal and distal colon by way of the rectum. These led out through a rubber funnel cemented to the skin around the anus. Air tight connections were then made with two water manometers and a gas burette. This provided a means of introducing measured quantities of gas and of recording pressure changes in the colons of unanesthetized dogs.

The tone of the colon remained unchanged regardless of the volume of gas present. The pressure was found to be slightly higher at the lower catheter, which might be explained by the accumulation of gas in the rectal region. Pressure changes accompanying contractions in the proximal and distal colon occurred, as a rule, simultaneously and were usually of the same magnitude. When large amounts of gas were administered, both the pressure during contraction and the frequency of contraction increased slightly.

These results indicate that the pressure is usually the same throughout the regions of the colon studied and that contraction probably causes a uniform change in pressure along the lumen of the intestine.

Excitability and recovery of responsiveness in sciatic nerves of hyperthyroid rats. FRANCISCO and ELENA HOFFMANN and JOHN F. PERKINS, Jr. (introduced by H. Davis). *Dept. of Physiology, Harvard Medical School, Boston.* Male rats were fed 1 to 1.5 grams daily of U.S.P. desiccated thyroid for periods varying from 34 to 62 days. Doses were omitted one day in seven. Muscle weakness resulted. Voltage-capacity curves were determined

on isolated nerves, using as end-point thirty per cent of the maximal action potential height.

There was no significant deviation between control and treated groups with respect to the shape of the curves, or to their position relative to the voltage parameter and the time parameter (or chronaxie).

Recovery of responsiveness was determined by stimulating with two slightly supramaximal shocks separated by varying intervals. Percentages of recovery, calculated from the height of the second response relative to the first, were plotted against intervals. The position and shape of the recovery curves were similar in both groups.

In conclusion, sciatic nerves of rats treated with massive doses of thyroid showed no changes with respect to excitability or to recovery of responsiveness.

The regulation of arterial blood pressure by vasomotor reflexes. J. P. HOLT, R. BERNSTEIN (by invitation), J. C. GREISEN (by invitation) and W. J. RASHKIND (by invitation). *Dept. of Physiology, Univ. of Louisville School of Medicine, Louisville, Kentucky.* Arterial pressure is a function of total peripheral resistance and cardiac output. An attempt has been made to determine how much of the pressor or depressor effect of various vasomotor reflexes is the result of a change in cardiac output and how much is the result of a change in peripheral resistance. In barbiturized dogs, with the vagus nerves sectioned, the cardiac output (modified Stewart method) and arterial pressure were measured and the peripheral resistance calculated before and during the stimulation of the carotid sinus, vagus, and sciatic nerves. Vagal stimulation gave an average increase in arterial pressure of +67%, in cardiac output of +15%, and in peripheral resistance of +47%. Carotid sinus nerve stimulation gave an average decrease in arterial pressure of -49%, in cardiac output of -14%, and in peripheral resistance of -41%.

The effect on cardiac output and arterial pressure of changing the peripheral resistance by making an arterio-venous shunt has been studied. A decrease in peripheral resistance by this method causes a fall in arterial pressure and an increase in cardiac output. The effect on arterial pressure and cardiac output of a simple decrease in peripheral resistance, brought about by making an arterio-venous shunt, will be compared to the effect on arterial pressure and cardiac output of a decrease in peripheral resistance brought about by means of a depressor vasomotor reflex. The relative importance of peripheral resistance and of the reservoir capacity of the venous system in the regulation of cardiac output and arterial pressure will be discussed.

An effort to demonstrate wrist stiffness in guinea pigs on a deficient diet. E. HOMBURGER

(by invitation) and C. I. REED. *Dept. of Physiology, Univ. of Illinois, Chicago Colleges.* A dietary factor essential for guinea pigs, absence of which produces wrist stiffness, had been described by Van Wagendonk in a series of papers. An attempt to demonstrate this factor was made by placing 40 pigs on the skim milk diet described by that author. At the end of 53 days, only 14 pigs survived. A daily supplement of 1 cc. of raw cream per pig to 5 pigs did not restore a healthy state; no more deaths occurred among 6 pigs continued on the diet up to 102 days. Three pigs given a normal diet ultimately resumed growth.

A second group of 42 pigs was placed on a diet of casein, yeast, starch and salt mixture as described (V. W. et al., *Arch. Biochem. 3: 305, 1944*). At 53 days, 16 pigs survived. Of 7 continued on the diet, 5 died by the 77th day; 5 pigs received a supplement of raw cream without influence on growth rate or condition. No wrist stiffness or joint tenderness could be demonstrated. Repetition of these experiments with 37 and 28 pigs respectively, likewise failed to produce stiffness, or any influence of raw cream on the condition of the pigs. We have, therefore, been unable to confirm the claim of a specific dietary syndrome, or the presence of a corrective factor in raw cream, since pigs in neither group recovered growth rates when the experimental diet was supplemented with raw cream.

**The influence of the ageing process on the distribution of phosphates and other components of the gastrocnemius muscle of the rat.** STEVEN M. HORVATH. *The Fatigue Lab., Harvard Univ.* There is a paucity of information defining the physiological and biochemical changes attending or resulting from the ageing process in mammals. Observers have commented on the striking reduction in muscular strength and activity in the aged. The gastrocnemius muscles of some 400 rats whose ages ranged from one to 780 days were analyzed for those phosphorus compounds concerned in muscular contraction.

It is only during the initial phases of the ageing process that changes are found. Large increases in the concentrations of solids, creatine, total phosphate, acid soluble and acid insoluble phosphates, hexosephosphates, phosphocreatine, and an undetermined phosphate of muscle are observed within the first thirty days of life. These increases continue at a slower rate for all of these components, except the total and acid insoluble phosphates, until constant levels are reached between sixty and 120 days of age. The changes with advancing age for total and acid insoluble phosphates are atypical. These rise to their highest concentrations in thirty days but immediately begin to diminish until the twentieth week of life when stable values are reached. The acid

insoluble phosphorous shows a slight tendency to rise with approaching senescence. A number of the components of muscle show no changes in concentration attributable to ageing. These include adenosine triphosphate, glycogen, orthophosphate and lactate. However, the constancy of the latter two components was not unexpected as they were used to indicate resting muscle. Adult and senescent animals have similar concentrations of all the compounds studied.

These findings indicate that the diminution in muscular strength and activity occurring in the aged cannot be attributed to lack of the compounds concerned with the chemical processes involved in muscular contraction.

**Growth retardation by a high protein diet after unilateral adrenalectomy.** EVELYN HOWARD and RICHARD S. BENTA (by invitation). *Dept. of Physiology, Johns Hopkins Univ., School of Medicine.* Young male mice with the left adrenal removed, on a high casein diet (protein 89% of total calories) showed a 31% retardation in body growth, as compared with similarly operated controls on 16% protein. Unoperated controls showed no statistically significant growth retardation on high protein diets.

No adrenal hypertrophy was observed on the high protein diets. After the left adrenal was removed, hypertrophy of the remaining adrenal occurred, but this was of the same amount in animals fed high and low levels of protein.

The failure of hypertrophy to occur on a high protein intake, in spite of the apparent functional disadvantage, suggests that the adrenal output might have undergone qualitative rather than quantitative change.

**A comparison of adrenal steroid diabetes and pancreatic diabetes in the rat.** DWIGHT J. INGLE, RUTH SHEPPARD (by invitation) and MARVIN H. KUIZENGA (by invitation). *Research Lab., The Upjohn Company, Kalamazoo, Mich.* Male rats of 300 grams or greater were force-fed a high carbohydrate diet. Glycosuria was induced in normal rats by the administration of 5 mgm. per day of either 17-hydroxyecdysterone or 17-hydroxy-11-dehydrocorticosterone. Similar animals were made diabetic by partial pancreatectomy. The onset of glycosuria in either adrenal steroid or pancreatic diabetes was accompanied by an increase in urinary nitrogen, loss of weight and a temporary increase in the excretion of sodium and chloride. The two types of diabetes were unlike in at least two respects: 1. Adrenal steroid diabetes but not pancreatic diabetes was highly resistant to control by insulin. 2. Following the beginning of the administration of the diabetogenic steroids there was a definite increase in urinary nitrogen which preceded the onset of glycosuria. In the depancreatized animals there was no increase in the level

of urinary nitrogen following the withdrawal of insulin until the glycosuria had become severe.

A ketonuria was observed in one animal having adrenal steroid diabetes and in several depancreatized animals.

**The value of supplemental alkalinizing therapy in hemorrhagic shock.** RAYMOND C. INGRAHAM and HAROLD C. WIGGERS. *Dept. of Physiology, Univ. of Illinois, College of Medicine.* Levine and co-workers have again emphasized the importance of shock acidosis in reporting marked beneficial effects from therapy involving correction of this condition. This was demonstrated in hemorrhagic shock by supplementing the re-infusion of withdrawn blood with alkalinizing agents ( $\text{NaHCO}_3$  and  $\text{Na Lactate}$ ).

Utilizing the method previously described by the authors (Am. J. Physiol. 143: 126, 1945) for the production of the irreversible shock state, the value of such supplemental alkalinizing therapy was studied. Under local novocaine anesthesia, dogs were bled rapidly (10-15 min.) until a blood pressure of 40 mm. of Hg was reached; this period of hypotension was maintained for 90 minutes. Following this, only the withdrawn blood was returned in the control series. Only 3 of 13 animals survived. In the present series, the reinfused blood was supplemented in 7 animals with  $\text{NaHCO}_3$ , plus glucose, in 6 animals with  $\text{Na Lactate}$  plus glucose, in quantities recommended by Levine. Again only 3 of 13 animals survived. Plasma  $\text{CO}_2$  capacities immediately prior to infusion were generally higher than those reported by Levine (15.6-24). Immediate post-reinfusion blood pressures equalled or exceeded pre-hemorrhage values and were generally more satisfactory than those observed in the control animals. Likewise, the survival time of the animals receiving supplemental therapy was definitely longer than that observed in the control series and the number of precipitant shock deaths was greatly reduced.

It appears then, that the use of supplemental alkalinizing agents provides only minor and temporary benefit and does not favorably effect the subsequent recovery of animals in hemorrhagic shock.

**Graphic registration of the effect of vaso-active drugs.** BENJAMIN JABLONS (introduced by Otis M. Cope). *2nd Medical Division, Goldwater Memorial Hospital, New York City.* It has been possible to obtain a graphic record of the effect of vasoconstrictor and vaso-dilator extracts and drugs on the peripheral circulation of animals and man by the use of a photo cell and light source placed on the opposite sides of translucent tissue and connecting the leads from the photo cell to a recording amplifying electronic galvanometer. The flow of blood in the narrowed or dilated vessels modifies the passage of light through the tissues and this in

turn is reflected in the variation in current set up in the photo cell. With this method studies have been made of the spontaneous fluctuation in the blood flow in the rabbits ear and in the human ear, finger and toe. Following the injection of vasoconstrictor drugs such as adrenalin and ergotamine there is a corresponding reduction in the amplitude of the tissue pulse whereas with the use of vaso-dilator substance such as the nitrites, nitro-glycerine and papaverine, etc., there is a marked increase in tissue pulse amplitude. This method has likewise been used to estimate the potency of renal extract preparations containing pressor and anti-pressor substances. Renin and renipressin (deproteinated) show vaso-constrictor effects on the peripheral circulation whereas tubulin the renal anti-pressor substance shows a marked increase in the amplitude in the peripheral pulse of the rabbit ear and the human ear, finger and toe. The latter effect differs from papaverine and the nitrites by its prolonged duration, lasting from 1 to 3 days after injection in both rabbits and humans. Renipressin similarly produces a vaso-constrictor effect which persists over a period of several days. It is also possible to obtain a graphic record of the systolic pressure by noting point at which release of cuff compression around the rabbit ear or arm in the human permits pulsation to be recorded.

**Bioassay of tubulin.** BENJAMIN JABLONS (by invitation) and OTIS M. COPE, *Dept. of Physiology and Biochemistry, New York Medical College, Flower and Fifth Avenue Hospitals.* A bioassay of the deproteinated anti-pressor substance derived from animal kidney has hitherto been very difficult because of the large amount of material required and the number of hypertensive animals necessary for such a test. Tubulin has been found to have a characteristic effect on the frog heart which has made it possible to utilize this preparation for the bioassay of this material. These tests show tubulin to be a gamma substance. This preparation has likewise been utilized for the study of renin, hypertensin, and renipressin. The antirenin effect of tubulin previously reported on nephrectomized cats has likewise been demonstrated in this preparation and has also been utilized for the bioassay of renin.

**The effect of phthalic acid on the prothrombin time in dicumarol-treated dogs.** L. B. JAQUES and A. P. DUNLOP (by invitation). *Dept. of Physiology, Univ. of Toronto.* Kudriashov (cf. J. A. C. S. 65: 2164, 1943) has reported that phthalic acid and derivatives have a marked antihemorrhagic activity in rats with ligated bile ducts. Dogs were given 10 mgm./kgm. of dicumarol intravenously. Two days later they were given intravenous injections of sodium phthalate. Small doses of phthalate had no effect on the prothrombin time. A single injection of 40 mgm./kgm. consistently

aused a fall in prothrombin time (e.g. from 80" o 45") when combined with a continuous injection of 10-30 mgm./kgm./hour. The fall in prothrombin time occurred within 10 minutes after administration of the phthalic acid and lasted for 10 minutes. Sodium phthalate added to the blood *in vitro* did not shorten the prothrombin time, and nephrectomy or evisceration had no effect on the action of sodium phthalate *in vivo*.

Identification of gun-shyness with experimental neurosis in dogs. A. V. JENSEN (introduced by W. F. Windle). *Cornell Behavior Farm, Ithaca, and Inst. of Neurology, Northwestern Univ. Medical School, Chicago.* The behavior of gun-shy dogs was studied for a period of time outside the laboratory and the animals were later subjected to conditioned reflex tests in the laboratory. The results of the laboratory tests indicate that the nervous condition of which gun-shyness is a symptom is so similar to experimental neurosis as to justify its identification as such. The principal deviations from normal were as follows: failure to establish an overt conditioned reflex, restlessness in the interval between stimulations, over-reaction to stimuli, immobility of the limbs throughout the test, hypersensitivity to touch, irregularities in the respiratory pattern, persistent nervous panting, deceleration of the respiration during the stimulus, persistent tachycardia in the interval between stimulations, and deceleration of the heart rate during the stimulus.

The simultaneous inhibition of overt muscular reaction, heart rate and respiratory rate during a stimulus which normally brings forth simultaneously muscular exertion, cardiac acceleration, and respiratory acceleration, suggests an interesting similarity between the symptoms of the nervous disturbance in the animals in which it occurred and the symptoms often seen in psychotic and psychoneurotic patients where the obvious repression of overt manifestations of an emotional state is accompanied by markedly increased autonomic function.

The nature and control of reactions in bioluminescence; with special reference to the mechanism of reversible and irreversible inhibitions by hydrogen and hydroxyl ions, temperature, pressure, alcohol, urethane and sulfanilamide in bacteria. F. H. JOHNSON, H. EYRING (by invitation), R. STENLAY (by invitation), H. CHAPLIN (by invitation), C. HUMER (by invitation) and G. GUERRANI (by invitation). *Depts. of Biology and Chemistry, Princeton Univ., Princeton, N. J.* The available evidence indicates that in *Cypridina* extracts and in bacteria, luminescence intensity ( $I_1$ ) is proportional to the rate of luciferin ( $LH_2$ ) oxidation by luciferase ( $A$ ) in presence of  $O_2$ . Excitation of  $L$ , followed by radiation, occurs in an electron transfer between semi-oxidized

molecules, from  $AL^-$  to  $LH$ . Inhibitions by  $H^+$  and by  $OH^-$  are largely reversible over a wide pH range. The pH-activity curve for luminescence of *P. phosphorum* in phosphate buffered isotonic NaCl solution is given by the equation:

$$\log \left( \frac{I_{\text{optimum pH}}}{I_{\text{other pH}}} - 1 \right) = K_{H^+}[H^+] + K_{OH^-}[OH^-]$$

in which the equilibrium constant  $K_{H^+} = 4.84 \times 10^4$  and  $K_{OH^-} = 4.8 \times 10^5$ , and the pH optimum = about 6.5.

The relation between luminescence intensity and pH varies with both temperature and pressure. At extremes of pH and normal optimum temperature, irreversible inhibitions occur. At above-optimum temperatures, destruction occurs most slowly at about pH 6.5, by a reaction that is independent of the reversible temperature inactivation of the system. Hydrostatic pressure tends to counteract both the reversible and irreversible inactivations.

Reversible inhibitions by sulfanilamide resemble the reversible effects of hydrogen ions, except for a pressure insensitivity. The inhibitions by both agents decrease with rise in temperature.

Reversible inhibitions by urethane and by alcohol increase with rise in temperature, and are largely counteracted by pressure. The chemistry of enzyme-inhibitor combinations is discussed, and theoretical formulations derived for analyses of quantitative data.

Factors controlling intramyocardial pressure. J. RAYMOND JOHNSON. *Dept. of Physiology and Pharmacology, Long Island College of Medicine.* In order to understand better the effects of myocardial contraction on coronary blood vessels and blood flow, and attempt has been made to analyze and evaluate certain factors which control this compression effect.

Intramyocardial pressure changes have been recorded optically from artery segments imbedded in the wall of the left ventricle during altered dynamics of the heart beat. These changes have been correlated with changes in the ventricular volume and compared with certain measurements obtained from skeletal muscle. The factors considered in the analysis and the deductions reached may be summarized as follows:

(1) Initial length of muscle fibers. Increasing initial volume in the left ventricle increases its capacity for developing higher intramuscular pressure, but the pressure actually developed depends upon conditions during the contraction.

(2) Resistance to muscle shortening. With increasing aortic resistance contractions of the left ventricle become more nearly isometric and intramuscular pressure approaches a measure of the full force of contraction.

(3) Contracted length of muscle fibers. Other

factors remaining reasonable constant, myocardial compression at any level varies inversely with ventricular size at the end of systole.

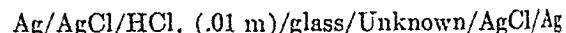
(4) Rate of muscle shortening. Changes in intramyocardial pressure accompanying alterations in the rate of ventricular emptying indicate that the gradient of pressure from endocardium to epicardium is probably an uneven one throughout most of systole and may alter appreciably with various dynamic changes.

**The acid-base binding properties of normal and pathological synovial fluid.** NORMAN R. JOSEPH (introduced by C. I. Reed). *Dept. of Physiology, Univ. of Illinois, Chicago Colleges.* The acid-base titration curves of normal and pathological human synovial fluid were determined on small samples of natural and electrodialyzed specimens. Specimens free of chloride and base were prepared by electrodialysis of a small volume (1 to 5 cc) of fluid with a mercury anode and cathode and cellophane membranes. The pH of the resulting preparation is taken to represent the composite isoionic point of all the non-diffusible components, and as the point of zero acid-base binding. The material is titrated with 0.1 N HCl or KOH over the pH range 2 to 11, with a glass electrode assembly. Titrations are also made with the natural fluid for comparison. From the data the base bound at the natural pH of the fluid can be determined, and also the buffering capacity at any pH.

Normal fluids were obtained from autopsies performed on hospital cases within a few hours after death. The pathological cases were those of arthritis patients, the material being obtained by aspiration of the joint. The mean pH of the normal fluids is in the neighborhood of 7.3, while that of the pathological fluids is approximately 7.6, several of the values approaching a pH of 8. The base binding capacities of the two types of fluid do not greatly differ, and are of the order of 50 millimoles per liter. In the case of the natural fluid, it is about 10 millimoles per liter greater than that of the electrodialyzed fluid, because of the removal of the diffusible buffers, phosphates and carbonates. The buffering power of the normal fluid is poor in the physiological and alkaline range, but high in the acid range, while in the pathological fluids it is quite high over the entire range. The composite isoionic point of the normal fluid is at pH 3 or lower. That of the pathological fluids is in the neighborhood of pH 4. These differences can be interpreted as being due to the presence of a relatively high concentration of indissoluble acid polysaccharide in the normal as compared with pathological fluid, and a high concentration of protein in the latter.

**The determination of the pH of animal tissues with a needle reference electrode.** NORMAN R. JOSEPH and EDMUND HOMBURGER (both introduced by C. I. Reed). *Dept. of Physiology, Univ. of Illi-*

*nois, Chicago Colleges.* A micro cell without liquid junction, consisting of a glass electrode and a silver-silver chloride electrode, is assembled in the following manner. An 18 or 20 gauge stainless steel needle is insulated on the outside, and the lumen is electrolytically plated with silver and finally with silver chloride. The glass electrode is prepared as a fine sealed capillary containing standard dilute HCl and an Ag-AgCl electrode. This is inserted into the needle reference electrode, the sealed tip flush with the tip of the needle, the two half elements forming the cell:



The E.M.F. of the cell is determined with a sensitive electrometer. It is related to pH by the equation

$$E = E^\circ + \frac{4.606 RT}{F} p\text{HCl}$$

where

$$p\text{HCl} = \frac{1}{2}p\text{H} + \frac{1}{2}p\text{Cl}$$

by definition.  $E^\circ$  is the standard potential of the cell, determined in a solution of known pHCl.

Measurements on blood, body fluids or tissues have been made, using rats or dogs. Values of pHCl have been obtained on the following: arterial and venous blood, peritoneal fluid, peritoneal fluid, muscle, synovial fluid, and heart. Values of pH can be derived wherever pCl can be independently estimated. Changes of pH produced by injection of dilute acid or alkali into various tissues have been studied with the electrode. Because of the small dimensions of the assembly, minute, sharply localized penetrations can be made without surgical procedures, and with a minimum of injury. Rapid determinations are possible.

**The relation of basal metabolic rate in students to the results of various tests for physical fitness and mental staleness.** FREDERIC T. JUNG, LILLIAN E. CISLER (by invitation) and MASON S. MAYNARD (by invitation). *Dept. of Physiology, Northwestern Univ. Medical School, Chicago.* The subjects were 37 volunteers, aged 18 to 25 years, who were beginning their first quarter in medical school. They filled out an enthusiasm-staleness questionnaire, took the Flack neurocirculatory test, had a basal metabolic rate determination on each of two occasions separated by an interval of 3 to 5 days, and gave blood for determinations of cell-pack volume, sedimentation rate, and differential leucocyte count. The enthusiasm-staleness score (ESS) gave satisfactory self-correlations as well as positive correlations with other measures of aptitude and scholarship, but was negatively correlated with all the desirable physical measurements such as the hematocrit reading and positively correlated with

undesirable scores like high lymphocyte percentage and fast pulse. The BMR's at the first session averaged  $-5.9\%$  and at the second  $-6.3\%$ ; they confirmed the prevailing belief that either medical students run below the average for the general population or that the standards are too high. High scores in the Flack test were positively correlated with other indications of unfitness such as sub-standard weight, high lymphocyte percentage, low hematocrit reading, and high BMR. The strongest correlation found was that relating high lymphocyte percentage to low hematocrit; this correlation was also found in data collected by Hepler from the records of 160 dispensary patients.

**Pulse reaction to step-up exercise on benches of different heights.** PETER V. KARPOVICH, MAJOR EDWIN R. ELBEL, Air Corps (by invitation), LT. E. L. GREEN, Air Corps (by invitation), CORPORAL R. R. RONKIN, Medical Dept. (by invitation) and ANNETTE F. MCLEMORE (by invitation). *AAF School of Aviation Medicine, Randolph Field, Texas.* Step-up exercises are becoming increasingly important in the testing of muscular proficiency and cardiac response of convalescent patients. Since the test using 24 steps per minute on a 20-inch bench (J. A. M. A. 126: 873 (Dec.) 1944) is too strenuous for some rheumatic fever patients, the use of lower benches was suggested. In order to determine the pulse reaction of normal individuals to exercise on benches of different heights, the present study was undertaken. Seventy-two healthy aviation students were each tested 10 times, once for 30 seconds and once for 60 seconds on benches of 5 different heights (12, 14, 16, 18, and 20 inches). Half-minute pulse counts were taken before, immediately after, and one minute after exercise. Testing order was randomized and thus was eliminated as a factor influencing pulse response. The average pulse rate immediately after 30 seconds of exercise was 3.7 beats per minute greater for each 2-inch increase in height of bench; after 60 seconds, the average increment was 5.6 beats per minute for each 2-inch increase in bench height. The pulse rate one minute after exercise generally fell below the resting pulse, except that it was slightly above the resting pulse after 60 seconds of exercise on the 20-inch bench.

**Studies on the innervation of the guinea-pig heart.** CORNELIUS T. KAYLOR (introduced by Jane S. Robb). *Dept. of Anatomy, Syracuse Univ. College of Medicine, Syracuse, N. Y.* The present work consists of a study of serial sections of the guinea pig heart stained by the Cajal silver nitrate method. This allows a differential staining of the nerve fibers to the heart; the sympathetic post-ganglionic fibers appear yellow while all other fibers stain brown to black.

It has been demonstrated (Nonidez, '39, '43) in the dog, cat, and monkey heart that the bulk of

the deeply stained parasympathetic postganglionic fibers end on structures above the coronary sulcus, i.e. on the nodes of the conductive system, the arteries and myocardium of the atria and auricles. The lightly stained sympathetic post-ganglionic fibers supply chiefly the ventricles.

In the guinea pig, it was observed that most of the deeply stained fibers are distributed to the A-V node, the main bundle and the bundle branches even out into the lateral walls of the ventricles. In contrast to the distribution of dark fibers to the ventricles, the atrial musculature and S-A node are sparsely supplied with deeply stained fibers. The course of the postganglionic sympathetic fibers could not easily be followed.

When the vagi are stimulated with weak currents in guinea pigs under pentobarbital anesthesia, the electrocardiogram indicates that the ventricles are affected sooner and to a greater extent than the atria. Thus the physiology of this heart is in accord with the anatomical distribution of presumably parasympathetic fibers.

**Selective and enduring dysreflexia following transections of the upper brain stem.** ALLEN D. KELLER. *Dept. of Physiology and Pharmacology, Baylor Univ. College of Medicine.* On the basis of "gross clinical inspection," a profound and enduring dysreflexia invariably follows a transection of the brain stem at any level through the midbrain and upper pons. This dysreflexia is selective to the extent that the reflexes which are eliminated or depressed vary with the level of the brain stem transections. Preparations having transections at various levels have been studied up to ten weeks after operation.

The scratch and crossed extension responses are permanently eliminated by a transection at any level of the midbrain and upper pons. The standing reflex, muscle tonus, the shake reflex, and the flexion response are permanently eliminated, only when the transection passes appropriately through the cephalic pons. Transections through the midbrain do not materially alter muscle tonus, the standing reflex, or the shake reflex; whereas the flexion response is either absent or very weak during the acute stage, but eventually returns to near normal. The corneal, swallowing, and cough reflexes exhibit some depression immediately following transections at the above-mentioned levels, but eventually return to normal or near normal.

The reflexes which were least disturbed were the knee jerks, urine voiding, and defecation reflexes. Erratic knee jerks were encountered on only one or two occasions, and these in atonic preparations. In these instances, there was a temporary depression only, and the tendon response eventually returned

\*Aided by a grant from the John and Mary R. Markle Foundation.

to normal. Most of the preparations having transections through the cephalic pons exhibited bilateral knee jerk responses, i.e. both of the legs jerked when only one tendon was tapped.

Certain of these observations have been reported previously (*Am. J. Physiol.* 123: 115, 1938; 126: 552, 1939).

**A brain stem mechanism for facio-vocal activity.** A. H. KELLY (by invitation), L. E. BEATON (by invitation) and H. W. MAGOUN. *Dept. of Anatomy and Inst. of Neurology, Northwestern Univ. Medical School, Chicago.* On the basis of clinical cases in which the two have been dissociated, it has been suggested that the neural control of the facial and vocal musculature is a dual one, involving both a cortical mechanism for volitional innervation and a sub-cortical mechanism concerned with the initiation of facio-vocal activity in the expression of emotion.

The potentialities of this postulated sub-cortical mechanism have been studied after chronic brain stem lesions produced in cats chosen for their normal or exaggerated display of facio-vocal activity upon nociceptive stimulation or when confronted with other animals.

Facio-vocal activity was still exhibited after lesions destroying the entire caudal hypothalamus or large areas of the midbrain at the level of the rostral portion of the superior colliculi, or after complete transections through the rostral midbrain. These results indicate that its mechanism must exist below diencephalic or rostral midbrain levels.

All facio-vocal activity was abolished after lesions destroying the central grey and adjacent tegmentum at levels through the caudal part of the superior colliculi. Similar results followed large lateral tegmental lesions more caudally placed at the transition level from the inferior colliculi to the pons.

This midbrain and pontile region, the destruction of which was followed by a loss of facio-vocal behavior, includes that area in which direct stimulation had previously been found to yield facio-vocal responses. The two lines of evidence seem both to demonstrate the presence of a sub-cortical facio-vocal mechanism and to indicate its midbrain and pontile position.

**The size of the human heart as a physiological variable.** ANCEL KEYS and ANGIE MAE STURGEON (by invitation). *Laby. of Physiological Hygiene, Univ. of Minnesota, Minneapolis.* Systolic heart sizes in normal young men were measured from posterior-anterior teleroentgenograms. Volumes were calculated as in *Amer. J. Roentgen. Rad. Ther.* 44: 805 (1940). Reliability of a single volume estimation was calculated from 85 pairs of films; the correlation was 0.99 and the standard deviation between duplicates was  $\pm 15.97$  ml. In 22 experiments the heart size was larger in the

seated as compared with the standing position (volume: 590.2 versus 552.7 ml., transverse diameter: 11.50 versus 11.23 cm.) The standard deviations of the differences were  $\pm 7.11$  ml. and  $\pm 0.077$  cm., with t values of 5.277 and 3.418, respectively. Three days of hard work without food (5 experiments) caused a reduction in volume (537.0 to 466.8 ml.) and transverse diameter (11.35 to 10.31 cm.). Standard deviations of these differences were  $\pm 15.70$  ml. and  $\pm 0.132$  cm., with t values of 4.47 and 7.92, respectively. Three weeks of bed rest (11 experiments) produced a decrease in volume (581.6 to 478.1) and transverse diameter (11.74 to 10.45). Standard deviations of these differences were  $\pm 13.38$  ml. and  $\pm 0.160$  cm., with t values of 7.74 and 8.06, respectively. The reduction in heart volume in the starvation experiment is significant at the 2% level. All other differences noted above are significant at the 0.3% level or better.

**Body size and energy metabolism during pregnancy of normal and precocious rats.** MAX KLEIBER and H. H. COLE (by invitation). *College of Agriculture, Univ. of California, Davis.* At the 13th and at the 20th day of pregnancy the metabolic rate after 16 hours of fast was measured on normal rats and on rats precociously sex-matured by injection of equine gonadotropin. Virgin rats served as controls.

At the 13th day of pregnancy the metabolic rate per unit weight of the normal rats was increased 16 per cent. The corresponding metabolic increase in precociously pregnant rats was only 5 per cent and was statistically insignificant. At the 20th day of pregnancy the metabolic rate per unit weight of the normal rats was 9 per cent above the corresponding rate for virgin controls, a difference statistically not quite significant. At this state of pregnancy the precocious rats had the same metabolic rate per unit weight as their virgin controls.

Microrespiration trials on uterus tissue combined with results of earlier measurements on fetuses were used to estimate for the metabolic rise during pregnancy a partition between fetal tissue, uterus, and the rest of the maternal body.

Contrary to the surface law theory of pregnancy metabolism our results indicate that pregnancy stimulates the metabolic rate in maternal tissues aside from uterus. Diaphragm slices from mature rats in mid pregnancy has indeed a 10 per cent higher rate of oxygen consumption in vitro than diaphragm slices from virgin controls.

**The effect of hemorrhage upon the amino nitrogen concentration of the blood.<sup>1</sup>** D. L. KLINE (in-

<sup>1</sup> This work was done under a contract, recommended by the Committee on Medical Research, between the Office of Scientific Research and Development and Columbia University.

roduced by M. I. Gregersen). *Dept. of Physiology, College of Physicians and Surgeons, Columbia Univ.* Fatal hemorrhagic shock was produced by Valeott's method (1944) in dogs in which a modified London cannula had been placed on the portal vein. Samples for amino N analyses were drawn simultaneously from the portal and hepatic veins and from the femoral artery and vein. The arterial-femoral venous differences, the arterial-portal venous differences, and the portal hepatic venous differences could thus be obtained to measure the changes in amino N concentration as the blood flowed through the leg, gut, and liver respectively.

After hemorrhage the amino N concentration increased steadily reaching its highest value terminally. The arterial-femoral venous differences, which were zero before bleeding, increased following hemorrhage and then fell terminally. The venous concentration was always higher than the arterial, demonstrating addition of amino N to the blood by the tissues of the leg. The portal concentration was consistently higher than the arterial, showing a progressive addition of amino N from the gut. Also the portal concentration of amino N was always higher than that observed in the hepatic venous blood, indicating the removal of amino N by the liver. Although the portal-hepatic differences rose steadily up to the end, this did not prevent the rise in arterial concentration of amino N.

**Age and sex differences in resistance to anoxia.** R. F. KLINE (by invitation) and S. W. BRITTON. *Dept. of Physiology, Univ. of Virginia Medical School, Charlottesville.* Responses to anoxia of different age and sex groups have been studied. Rats (sex studies), cats, dogs and opossums were used. In most cases a reduced barometric pressure of 320 mm. Hg (22,000 ft. alt. equivalent) was employed in closed chambers, at controlled environmental temperatures.

The youngest age groups—fetal or newborn animals—showed extremely long survival periods, ranging from 25–50 hours in some cases. Brief survivals similar to those of the adult animal were not observed until about weaning age.

Marked sex differences in survival of rats to anoxia were observed over a wide chamber temperature range. At the lower air temperature levels, c. 16°, females withstood anoxic exposure from 25 to 50 per cent longer than males; averages of 190 mins. for males and 260 mins. for females were found, using the closed chamber method. The curves of survival gradually approximated at higher temperatures, but some differences were apparent even at 33°. Similar sex differences were noted when through ventilation was employed at higher altitude equivalents.

Estrous conditions and estrogens, castration, etc., do not appear related to the different responses.

**Effects of alteration of blood pH on electrical excitability of the nervous system.** HAROLD KOENIG (introduced by W. F. Windle). *Inst. of Neurology, Northwestern Univ. Medical School and The Chicago Medical School, Chicago.* Cats anesthetized with chloroform were made acidotic slowly with a lactate buffer administered by venolysis. Stimulating electrodes were placed on peripheral nerves and, by means of the Horsley-Clarke stereotaxic instrument, in cell groups in the brain. Blood pH was followed throughout the experiment. Stimulation thresholds for elicitation of the various appropriate responses were determined before administration of the buffer and at intervals as blood pH was falling. Normal pH was about 7.50; minimum obtained was 6.75.

The threshold for motor nerves remained unchanged. The threshold for cranial motor nuclei was unchanged, or slightly altered when the pH was kept at a low level for a considerable period of time. The threshold for the facial motor cortex rose at higher pH values and to greater extent than did that for the facial nucleus. Threshold for a reflex response mediated through the sciatic nerve upon stimulation of the saphenous nerve was the most greatly affected. Previous section of the spinal cord in the thoracic region did not change this latter observation.

Significant changes in electrical excitability occurred when the pathway consisted of more than one neuron. Excitability was diminished in proportion to the decrease in blood pH. The effects were reversible. [Aided by a grant from the National Foundation for Infantile Paralysis, Inc.]

**The effect of various types of electrical stimulation and of frequency of stimulation upon muscle atrophy in the rat.** A. J. KOSMAN (by invitation), S. L. OSBORNE and A. C. IVY. *Dept. of Physiology, Northwestern Univ. Medical School, Chicago, Ill.* The sciatic nerve was sectioned bilaterally in three groups of 15 rats each. In one group, the denervated gastrocnemius on one side was stimulated with an "interrupted galvanic" current; in a second, with a "slow sinusoidal" current and in a third, with a 25 cycle alternating current. Each group was treated once daily for 28 days following denervation at which time the animals were sacrificed and both gastrocnemii weighed. The mean difference in per cent between treated and untreated muscles for each group was: "interrupted galvanic":  $\pm 19.5$  per cent; "slow sinusoidal":  $\pm 3.2$  per cent; 25 cycle A.C.:  $\pm 51.5$  per cent. The greatest retardation of weight loss was obtained with the 25 cycle A.C. Of the other two types of current, both of which are in common clinical use, the "interrupted galvanic" is apparently more effective.

In 5 groups of 10 rats each the gastrocnemius on one side was stimulated with a 25 cycle A.C. as follows: Group A: once daily for 10 minutes;

rise of blood pressure produced by renin in the intact animal.

These results suggest that in the course of producing vasoconstriction in the intact rabbit hypertension is withdrawn rapidly from the general circulating blood probably by combination with the vascular smooth muscle, and that any hypertension not so combined seems to disappear too rapidly to permit assay by the rabbit's ear method. These findings help to explain the negative results usually obtained in assays of systemic blood from hypertensive animals or patients, and also for the negative results obtained in indirect transfusion experiments.

**Effect of structural modification on the anticholinergic action of some basic esters.** A. M. LANDS, V. LORAIN NASH (by invitation) and KATHRYN Z. HOOPER (by invitation). *Pharmacological Research Lab., Frederick Stearns and Company Division, Detroit, Mich.* A number of synthetic basic esters, described below, have been made available to this laboratory for investigation. Their action on isolated segments of rabbit jejunum was determined according to the method of Magnus.  $\beta$ -Diethylaminoethyl acetate (I), 1-100,000 cause acetylcholine-like contractures that are readily relaxed by atropine sulfate. When acetylcholine, 1-1,000,000 or I, 1-100,000, are used to induce contraction, these contractures may be relaxed as indicated below.

**$\beta$ -Diethylaminoethyl**

glycolate (II), 1-10,000 to 1-20,000

phenylacetate (III), 1-100,000

phenylglycolate (IV), 1-200,000 to 1-500,000

cyclohexanacetate (V), 1-200,000 to 1-500,000

cyclohexanglycolate (VI), 1-500,000

diphenylacetate (Trasentin) (VII), 1-500,000 to 1-1,000,000

phenyl- $\alpha$ -thienylacetate (VIII), 1-5,000,000

diphenylglycolate (IX), 1-40,000,000 to 1-50,000,000

phenyl- $\alpha$ -thienylglycolate (X), 1-60,000,000

cyclohexyl- $\alpha$ -thienylglycolate (XI), 1-80,000,000 to 1-100,000,000

Atropine sulfate, 50,000,000 to 100,000,000

From the above, it will be noted that the unsubstituted acetic ester is cholinergic and becomes anticholinergic (antispasmodic) when one or more of the hydrogen atoms are replaced. The substitution of an hydroxyl for one of the hydrogens as in II results in a compound that does not stimulate the isolated jejunal segment and will abolish contractures induced by I. The substitution of phenyl, cyclohexyl or  $\alpha$ -thienyl groups for the hydrogens of the methyl group of the acetate further increases the antispasmodic potency against contractures induced by acetylcholine or I. Compounds contain-

ing the  $\alpha$ -thienyl group appear to be more anticholinergic than their corresponding phenyl analogs. Thus VIII > VI, X > IX, and maximum activity is found in XI. Greatest activity is obtained with the trisubstituted acetates X and XI wherein each substituent differed from the other. These latter substances equalled or exceeded atropine in their action on the jejunum. Anticholinergic action on the salivary glands, iris, and cardiovascular system was determined and comparable results were obtained. Compounds II to VI exerted little or no demonstrable anticholinergic action in these organs, VII and VIII were anticholinergic in relatively high concentration and IX, X and XI were anticholinergic in relatively low concentration. (Compound II was prepared from the crude hydrochloride, III from the free base, from which a hydrochloride solution was prepared. All others were prepared from the hydrochloride salts.)

**Effect of withdrawal and injection of cells on the apparent total circulating cell volume.** HAMPTON LAWSON and W. S. REHM (by invitation). *Dept. of Physiology, Univ. of Louisville School of Medicine, Louisville, Ky.* Plasma volume was estimated as the dilution volume of the dye T-1824 in intact barbitalized dogs. Total cell volume was calculated from the plasma volume and the cell-plasma ratio in drawn blood. These measurements and calculations were repeated at intervals during a nearly complete controlled exsanguination, at the end of which whole blood or gelatin solutions were injected. Four hours later a second "direct" determination of plasma volume was made, and the animals were bled to death. Plasma and cell volumes were again estimated at intervals during the final exsanguination. Plasma volume measured at any time during either exsanguination was greater than the original volume minus the volume drawn. During the first bleeding the apparent cell volume was in some cases greater, in others less, than the original volume minus the volume drawn. Following the injection of cells, the average increase in circulating cell volume was about 29% greater than the volume of cells injected. There was no change following the injection of cell-free fluids. On the final bleeding, the average loss of cells was about 29% greater than the volume of cells withdrawn. These findings are consistent with the view that drawn blood has a higher cell-plasma ratio than the mean ratio for the cardiovascular system as a whole, after the splenic reservoir has been emptied.

**Blood proteins of normal and hypophysectomized rats in reference to high protein diet.** JAMES

H. LEATHEM (introduced by W. W. Swingle). *Dept. of Zoology, Rutgers Univ., New Brunswick, N. J.* Protein metabolism is influenced by the adrenal cortex. Moreover, a high protein diet may increase adrenal size and perchance influence gland function so that these studies on blood proteins were undertaken. Adult male rats were fed ad lib. a diet containing 83% protein (78% casein) over a 20 day period and blood protein level were compared with rats eating ad lib. a stock diet containing 33% protein. Blood NPN was above normal but total protein levels and plasma albumin and globulin concentrations were unaltered. Body weight increased normally. A similar experiment using 40 day old rats over a 54 day period yielded identical results. Adrenal hypertrophy was not observed.

Adult rats eating the stock diet but pair fed with rats eating the high protein diet exhibited a 20 gram decrease in body weight. The blood protein revealed a slight fall in total protein due to a decrease in albumin concentration.

Hypophysectomy is followed by a marked decrease in plasma albumin and an increase in plasma globulin concentration which is not influenced by offering a high protein diet to hypophysectomized rats eating ad lib.

The utilization of dark adaptation in airline transport pilots. L. G. LEDERER. *The Medical Dept. Pennsylvania-Central Airlines, Washington, D. C.* Utilizing the concept that red light interferes least with dark adaptation, installations were made on DC-3 standard Douglas.

Airline pilots using this installation report less fatigue to the eyes after night flights and a distinct ability to see the terrain below in greater detail than ever before. Difficulties have been encountered in that night vision is "washed out" when the pilot approaches a brightly lit terminal or when flying in thunderstorms wherein frequent lightning flashes produce distinct contrast in lighting conditions.

Studies made on developments in visual acuity after all-night flights with and without re-lighting do not show any distinct improvement in acuity when red lights are used and fall within the limits of experimental error. The beneficial results obtained, it is believed, have been due to improvement in night vision and a more rested, comfortable feeling in the eyes of pilots who have been engaged in night flight.

Considerable opposition has been encountered when pilots have not been adequately informed as to the merits of red cockpit lighting from a physiological standpoint. It is, therefore, necessary to precede any radical change in instrument placement or design by an educational program fully

explaining the physiological principles involved in understandable language. We feel that dark adaptation will be one of the major developments in modern aircraft cockpit lighting design. However, airport lighting should be closely co-ordinated with this program.

Thromboplastic activities of various preparations isolated from beef brain. JOSEPH LEIN and HARRY W. HAYS (introduced by W. W. Swingle). *Dept. of Pharmacology, Ciba Pharmaceutical Products, Inc., Summit, N. J.* Preparations of substances having thromboplastic activity were isolated from beef brain and assayed quantitatively. Activities were expressed as percentage decrease in coagulation time due to the thromboplastic agent.

The preparations were divided into two classes, (1) those containing protein and, (2) those consisting of phospholipids freed from protein contaminants. The protein preparations were more active than the lipid preparations; while, the crude phospholipids were more active than the purified. The lipid preparations reached a maximum activity which fall off at high concentrations in contrast to the protein preparations which maintained a plateau of activity at high concentrations.

A relatively potent lipid preparation could be isolated if precautions were taken to prevent the loss of active material through ethyl alcohol extraction and to protect it from auto-oxidation. The most potent lipid preparation isolated was identified as a mixture of cephalin and lecithin. While the activity of this mixture at optimum concentration was considerably less than that of the potent protein preparations, the minimum amount of material which caused a fifty per cent decrease in coagulation time approached that of the protein preparation.

The isolated phospholipid preparation could be stabilized through the addition of sufficient hydroquinone to prevent auto-oxidation. Preparations thus protected, retained their original color and activity for several months.

The influence of various endocrine states upon the rate of protein breakdown in the eviscerated rat. R. LEVINE, T. A. TEXIDOR (by invitation), A. L. ANRANS (by invitation) and S. SOSKIN. *Dept. of Metabolic and Endocrine Research, Michael Reese Hospital, Chicago.* The overall rate of protein catabolism is generally estimated from the nitrogen excretion in the urine. The change in this excretion rate gives no indication whether this is due to changes in the rate of protein → amino acid breakdown, or to an effect on deamination and urea production.

In order to separate these phenomena we have studied the influence of various endocrine states upon the rate of rise of blood amino acids in the

eviscerated rat. The Table shows the results when the rate of amino acid rise in the normal control animals is expressed as 100.

Condition	Rate of amino acid rise in blood
Normal.....	100
Diabetic (alloxan).....	404
Hyperthyroid (thyroxin).....	230
Hypothyroid (thiourea).....	42
Hypophysectomized.....	154
Adrenalectomized.....	95
Diabetic given insulin.....	46
Normal given insulin.....	22
Diabetic given large amounts of glucose .....	110

These results demonstrate that the increased rates of protein breakdown due to lack of insulin and reduced thyroid activity have a large peripheral component and can be demonstrated in the absence of the liver. Protein-sparing action of carbohydrate and insulin are also evident in the absence of the liver.

We are now engaged in estimating the rate of urea production in perfused rat livers, under various conditions, in order to assess the influence of carbohydrate and of endocrine states on the hepatic component of protein metabolism.

**Sympathomimetic action of methyl- $\beta$ -cyclohexylethylamine.** JOHN R. LEWIS (by invitation), ELEANOR E. RICKARDS (by invitation) and A. M. LANDS. *Pharmacological Research Lab., Frederick Stearns and Company Division, Detroit, Mich.* Methyl- $\beta$ -cyclohexylethylamine, synthesized by Blieke and Monroe (J. Am. Chem. Soc. 61: 91, 1939), is an active sympathomimetic amine. Intravenous administration of aqueous solutions of the hydrochloride salt into anesthetized dogs in a dose of 0.5 mgm./kgm. caused an average rise in blood pressure of 55 mm. Hg., an increase in heart rate of 37 beats/min. and an increase in amplitude of beat of 43 per cent. Tachyphylaxis was not observed with repeat injections. Recordings of the nasal

constriction in the nasal mucosa. There was a transient reduction in rate and depth of respiration at the time of maximum blood pressure rise. Isolated segments of rabbit jejunum were relaxed in dilutions of 1-50,000 to 1-100,000. In anesthetized dogs, there was a reduction in tonus and motility of the jejunum in situ concomitant with the rise in blood pressure which lasted as long as the pressure was elevated. The isolated non-pregnant rat uterus responded to dilutions of 1-40,000 to 1-200,000 by a reduction in both tonus and motility. The administration of relatively large doses intraperitoneally into rats caused no demonstrable stimulation of the central nervous system. Acute toxicity was determined by intraperitoneal injection into

albino mice. The LD 50 appears to lie between 115-125 mgm./kgm.

The free base of methyl- $\beta$ -cyclohexylethylamine has been synthesized by our Organic Research Department and supplied to us with the information that this substance is a colorless, relatively stable liquid, boiling at 76-77° C. at 8 mm. pressure and that it is insoluble in water but soluble in ordinary organic solvents. This material is volatile and has been tested as a volatile vasoconstrictor for the nasal mucosa. Preliminary investigation indicates that in this form it is equal or superior to equal or superior to  $\beta$ -phenylisopropylamine.

**The effect of diet on the susceptibility of rats to benzene poisoning.** TSAN-WEN LI (by invitation) and SMITH FREEMAN. *Dept. of Physiology, Northwestern Univ. Medical School, Chicago, Ill.* Four groups of young adult male albino rats, 7-10 per group, were exposed to 600 P.P.M. of commercial benzene for 42 hours per week, for 12 weeks. Four similar groups served as controls. Two groups, a control and an experimental group, were fed one of the following diets: (1) high-fat high-protein (HH), (2) low-fat high-protein (LH), (3) high-fat low-protein (HL), (4) low-fat low-protein (LL). Lard supplied 55 per cent of the calories on the high-fat diet and 30 per cent on the low-fat diet. Casein supplied 27 per cent of the calories on the high-protein diet and 8 per cent on the low-protein diet.

The exposed groups all gained less weight than the corresponding controls. The differences in weights were much greater in the low-protein groups. The exposed HL group lost weight during the experiment. The final weights for exposed groups were in the following order: HH > LH > LL > HL. The order in the control groups was HH > LH > LL > HL. The weight differences among the exposed groups were much greater than among the controls. Leucopenia occurred in all exposed groups and was more marked on the high fat diets. Anemia was present in all protein-deficient groups, and was similar in control and experiment groups. Food consumption of all groups was essentially the same except that the exposed low-protein groups ate less. Fatty livers were only found in protein-deficient groups and were more marked in the controls. [This study was assisted by a grant from the Velsicol Corporation.]

**The frequency of "peptic ulcer" in protein-deficient dogs.** TSAN-WEN LI (by invitation) and SMITH FREEMAN. *Dept. of Physiology, Northwestern Univ. Medical School, Chicago, Ill.* This is a summary of the autopsy findings on 32 dogs that were maintained on protein deficient diets until moribund. The synthetic diet which supplied 40 Cal. per pound of body weight daily was devoid of protein save for that contained in yeast, which made up 5 per cent of the diet. All autopsies were

performed immediately after moribund animals were sacrificed. Fifteen of these protein-deficient animals had "peptic ulcers", 13 had solitary ulcers of the duodenum near the pyloric sphincter and 12 had ulcerations on the pyloric side of the sphincter. Two other animals had superficial erosions of the gastric mucosa.

The survival period of these dogs varied from 6 to 22 weeks. No animals that survived less than 12 weeks had an ulcer, other than this fact there is no correlation with the time of depletion.

The incidence of ulcer in these animals did not seem to be correlated with any constituent of the diet, other than protein. Diets high and low in fat (33, 15 and 2 per cent) with or without cholesterol (0.1-0.2 gram/lb. body weight daily) or added bile salts (2.8 grams daily), caused a similar incidence of ulcer, nor could the dye clearance by the liver, elevation of serum phosphatase or fattiness of the livers be correlated with the frequency of ulcer.

**Position of carboxyl carbon of fed acetic acid in glucose from rat liver glycogen.** NATHAN LIFSON, VICTOR LORBER and HARLAND G. WOOD (by invitation). *Dept. of Physiology, Univ. of Minnesota Medical School, Minneapolis.* Buchanan et al. (J.B.C. 150: 413, 1943) after feeding glucose and carboxyl labelled radioactive sodium acetate to fasted rats, found radioactive carbon in the liver glycogen. From comparison of these results with those obtained after administering radioactive  $\text{NaHCO}_3$ , they concluded that all the labelled carbon appearing in the glycogen after such acetate feeding could be accounted for by  $\text{CO}_2$  fixation alone.

Since Wood et al. (in press) have found that after heavy carbon ( $\text{C}^{13}$ ) administration as  $\text{NaHCO}_3$  to rats, detectable labelled carbon appeared only in carbon atoms 3 and 4 of the glucose obtained from liver glycogen, it became of interest to determine whether the positions of the heavy carbon of such glucose after carboxyl labelled acetate feeding are the same as after labelled  $\text{NaHCO}_3$  administration.

Fasted rats were fed by stomach tube glucose and sodium acetate with excess heavy carbon in the carboxyl group of the latter. The livers were extirpated 2 to 3 hours later. The degradation products of the glucose obtained from the liver glycogen showed detectable excess  $\text{C}^{13}$  present only in carbon atoms 3 and 4 of the glucose, just as for  $\text{CO}_2$  fixation.

These results are consistent with exclusive incorporation of the heavy carbon into the glycogen by  $\text{CO}_2$  fixation, but they do not rule out other possible routes. To investigate this point further, preparations have been initiated for repetition of these experiments with the use of acetate with both carbon atoms labelled.

The oxygen-hemoglobin dissociation curves of

man determined *in vivo*.<sup>1</sup> J. L. LILENTHAL, JR. and R. L. RILEY (introduced by C. L. Gemmill). *School of Aviation Medicine, Naval Air Training Bases, Pensacola, Fla.* The relations of oxygen tension and oxyhemoglobin saturation have been determined in man over the physiological range by analysing arterial and venous blood drawn at rest without stasis under normal conditions, during anoxia, and during reflex vasodilatation. The tensions were determined by the bubble method (Riley, Fed. Proc., 1945) within 8 minutes after the blood was drawn. Oxyhemoglobin contents and capacities were determined by the Roughton-Scholander microgasometric technic. A portion of the blood was equilibrated rapidly with 100 p.c. oxygen and the analyses for oxyhemoglobin capacity begun within 4 minutes after the blood was drawn. The rapidity of these analyses reduced to probable insignificance the errors introduced by the reversion of inactive to active hemoglobin which occurs in shed blood (Roughton *et al.* Am. J. Med. Sci. 208: 132, 1944). The blood pH was not the same for all tensions, but varied within the normal physiological range.

The activity during contraction of different parts of the same mammalian muscle, *in situ*.<sup>2</sup> HANS LÖWENBACH and J. E. MARKEE (introduced by F. D. McCrea). *Depts. of Physiology and Neuropsychiatry and Dept. of Anatomy, Duke Univ. School of Medicine, Durham, N. C.* By a combination of photographic procedures the movements of exposed muscles *in situ*, "segmented" transversely by markers, were recorded in experiments on twenty dogs. Electrical stimuli were employed and sometimes movements were provoked by reflex action.

Isometric and isotonic contractions occur simultaneously in different "segments" of the same muscle. The ratio of the number of the isometrically to the isotonically contracted "segments" is never constant but varies as the distance between the points of attachment. Completely isometric contractions or completely isotonic contractions are obtained only by detaching one end of the muscle. This agrees with findings of Bethe, Happel and Fischer whose method is applicable only to the isolated frog muscle.

When normal or curarized muscle is stimulated directly, or when but one main branch of the nerve supplying the muscle is stimulated, the other branches having been cut, another phenomenon occurs. The part stimulated shortens and the parts

<sup>1</sup> The opinions or assertions contained herein are the private ones of the writers and are not to be construed as official or reflecting the views of the Navy Department or the naval service at large.

<sup>2</sup> Aided by a grant from the National Foundation for Infantile Paralysis, Inc.

unexcited by the stimulus show considerable stretch.

Approximation of the points of attachment occurs only if the amount of shortening in one part of the muscle exceeds all the stretch that might be present in other parts. Electrical stimulation of the entire nerve approximates the points of attachment. Less movement of the joint is produced by stimulation of any one of the main branches of the nerve, or by direct stimulation of the muscle, because the effect of shortening in one part is partially or completely cancelled by stretching in other parts.

**Experiments on tonal interference in the cochlea.** KARL LOWY (introduced by E. A. Culler). *Univ. of Rochester, Rochester, N. Y.* The phenomenon of tonal interference in the cochlea, as described by Wever, Bray and Lawrence, was studied in cats under nembutal anesthesia.

The results indicate that: 1) relative reduction of the cochlear potential due to presentation of a second tone diminishes soon after death, 2) in animals whose eighth nerve has been cut several weeks prior to the test, there is less cochlear interference, 3) the mutual interference of two tones which, applied alone, yield equal cochlear response, is not necessarily the same.

These observations make it somewhat doubtful if the problem of cochlear interference can be adequately treated without reference to neural interaction.

**Pattern of human cardiac response to centrifugal force.** C. A. MAASKE (by invitation), GEORGE L. MAISON and G. A. HALLENBECK (by invitation). *Physiological Branch, Aero Medical Lab., Engineering Division, AAF Air Technical Service Command, Wright Field, O.* Man is admirably adapted for life on a planet where the normal force of gravity is as it is on earth. If he is seated, his circulatory system is adequate in most cases to maintain his sensorium alert at three times normal gravity. The primary mechanism by which this is accomplished seems to be increased cardiac rate.

Centrifugal force has been used to simulate multiplication of normal gravity. (See description of accelerator under F. G. Hall). At the highest force level which over a ten second exposure did not produce visual changes the average increase in cardiac rate in 47 subjects was 27.42 per minute with a range from 13 to 47. At force levels which abolished peripheral vision heart rate rose (average) 31.65 per minute (range 3 to 53) in 47 subjects. When force was adequate to abolish central vision cardiac rate rose 34.11 per minute average (range 14 to 66) in 44 subjects. When the force is rapidly withdrawn at the end of the 10 seconds a bradycardia is the rule with strong "vagal" beats. On the other hand continuance of these force levels

beyond 10 seconds permits recovery of symptoms without accompanying further rise of cardiac rate.

**Toxicity of snake venom for developing frog larvae.** DAVID I. MACHT. *Pharmacological Division of the Sinai Hospital Labs., Baltimore, Md.* The toxicity of snake venoms in various concentrations was tested on larvae of *Rana Sylvatica* at various ages, from 2 days to 6 weeks old, during March and April, 1944. Venoms of five species of COLUBRIDAE (*Naja tripudians*, *Naja nivea*, *Bungarus fasciatus*, *micrurus fulvius*, and *Sepedon haemochates*) and of five species of VIPERIDAE (*Bothrops atrox*, *Crotalus ruber*, *Bites arietans*, *Agirodon mokasen*, and *Daboia*) were examined by dissolving the dry scales in physiological saline and then diluting with water. The pH of all the diluted solutions was the same as tested by the potentiometer. Tadpoles placed in control solutions lived for many days, while those immersed in venom solutions were more or less poisoned. In respect to potency, all the Colubrine venoms were very toxic, while all the Viperine venoms were much less so. For example, Tadpoles seven days old placed in solutions of Cobra and other Colubrine venoms 1:1000 died within 15 to 20 minutes, while those immersed in Viperine venom solutions 1:1000 succumbed in 8 to 15 hours. Remarkably, Colubrine venoms were even more toxic for older larvae, e.g. 35 days old, than for younger Tadpoles, e.g. 7 days old. This was not the case with Viperine venoms. Cobra neurotoxin solution, prepared according to Van Esveld, was nearly as toxic as solutions of crude venom of strength corresponding to its neurotoxin yield. The greater toxicity of cobra venom for older than younger tadpoles might perhaps be explained by the greater development of the C.N.S. in the former.

**Sensory effects of centrifugal force on man when seated.** GEORGE L. MAISON, C. A. MAASKE (by invitation) and E. E. MARTIN (by invitation). *Physiological Branch, Aero Medical Lab., Engineering Division, AAF Air Technical Service Command, Wright Field, O.* As of 1 January, 1945, 276 persons have been exposed to centrifugal force on the AAF human centrifuge during its 19 months in operation. The character of the exposures involves a rigid pattern in which the centrifugal force is brought as rapidly as possible to the peak force desired, maintained at that level for 10 seconds, and withdrawn as rapidly as possible. The actual rate of rise of force is between 2 and 3 gravitational units per second. (Details of the accelerator used will be found in a motion picture demonstration. See abstract under F. G. Hall.)

The outstanding sensory effects of centrifugal force on man are visual. Subthreshold levels averaged 3.4 gravitational units with a range from 2.6 "g" to 4.9 "g". Peripheral vision dimmed on the

average at 3.9 "g" with a range from 2.8 to 5.2. Peripheral vision was lost at 4.5 "g" (average), range 3.1 to 6.6. Central vision was lost at 5.0 "g", range 3.2 to 7.0. Complete abolition of sight and hearing occurred at 5.6 "g", range 4.0 to 7.0. Prolongation of a given force level beyond 10 seconds if it does not cause unconsciousness usually results in a recovery of the sensorium to a greater or lesser degree.

**Effect of arterial blood gases and pH of breathing oxygen under pressure at simulated high altitudes.** JOHN P. MARBARGER, C. BRUCE TAYLOR and MARSCHELLE H. POWER (introduced by W. M. Boothby). *Mayo Aero Medical Unit, Under Contract No. AC 25829 with Wright Field.* Two types pressure breathing equipment were used. (1) A pressure mask alone connected to demand oxygen regulator adjusted to function at pressures above ambient. (2) A closed circuit including pressure mask and inflatable jacket surrounding the chest and abdomen was used in experiments at 50,000 feet in which pressure exceeded ambient pressure by approximately 33 mm. Hg.

Experiments conducted in low-pressure chamber at room temperature: subject in recumbent position, operator sitting, standing, or moving. Duration of positive pressure breathing before puncture of the femoral artery varied up to 24 minutes. At pressures equivalent to altitudes of 41,000, 44,000, 46,000, and 50,000 feet, oxygen was delivered through the breathing equipment at pressures of 0, 13, 15, and 33 mm. Hg, above ambient, respectively. Under these conditions the means of the arterial oxygen saturations were 89.9, 88.5, 77.8, and 76.4 per cent, respectively; the means for carbon dioxide content were 45.7, 44.5, 46.1, and 43.4 volumes per cent; and means for pH were 7.41, 7.49, 7.46, and 7.46.

Oximeter readings were in good agreement with the per cent oxygen saturation as determined by gasometric analysis.

Results demonstrate pressure breathing to altitudes of 50,000 feet can maintain a tolerable oxygen supply, with but slight disturbance of bicarbonate equilibrium. Motion pictures of the arterial puncture technique taken at 50,000 feet showed subject and operator in good condition and the latter well coordinated.

**Fluid balance as influenced by carbon-dioxide.** EDWARD C. MASON. *Dept. of Physiology, Univ. of Oklahoma School of Medicine, Oklahoma City.* There are several lines of evidence which makes it impossible to interpret the behavior of body fluids in terms of simple osmotic relationship; "changes in the properties and activities of cytoplasm probably explains many of the changes in the distribution of body water" (Darrow). One of the most common products of tissue activity is carbon-

dioxide and therefore we have focused our interest on the action of this product.

The hydrophilic capacity of frog muscle was determined, with and without the presence of carbon-dioxide, using: distilled water, and graduated concentrations of the following; sodium chloride, ammonium chloride, hydrochloric acid, sodium hydroxide, glucose, urea, sodium bicarbonate, monobasic and dibasic sodium phosphate.

Frog legs were sectioned at the hip joint, skinned and the entire limb and foot were weighed and immersed in 100 cc. of fluid contained in 150 cc. beakers. The muscles were again weighed at the end of 4 hours and 20 hours. At the end of 20 hours they were subjected to an atmosphere of carbon-dioxide. In some experiments the muscle or the solutions were directly exposed to carbon-dioxide for various lengths of time before immersing the muscle.

Frog legs hydrated, in distilled water for 20 hours, lost approximately 42 percent of such hydration when subjected to an atmosphere of carbon-dioxide for 8 hours. Results obtained with solutions of the previously mentioned substances suggest that this action of carbon-dioxide is not due to acidity changes.

**Concerning the mechanism of aggravation of diabetes by infections.** EMILIO MATTAR (by invitation), R. LEVINE and S. SOSKIN. *Dept. of Metabolic and Endocrine Research, Michael Reese Hospital, Chicago.* The production of a sterile empyema (turpentine) in depancreatized dogs leads to an increase in the blood sugar level of these animals. It is, of course, well known that many types of infection lead to an aggravation of the diabetic state in humans. On the basis of simultaneous determinations of glucose, NPN, etc., of the whole blood and of the empyema fluid, Menkin contends that the concentration of these substances is significantly greater in the empyema fluid than in the blood. Therefore he concluded that the inflammatory focus is an added site of gluconeogenesis from protein and that this accounts for the rise in the hyperglycemia.

We have repeated these experiments in 10 dogs. However, we determined the glucose and NPN concentrations in the *fluid phases* of both the blood and the pleural effusion, since the cellular content of blood is always much greater than that of the effusion. The figures show that the concentrations of glucose and of NPN are essentially the same in the plasma and the supernatant portion of the pleural effusion. There is no evidence of any gradient of these substances between these two fluid compartments. In four dogs the liver was removed at the height of the inflammatory reaction. The rate of fall of the blood sugar was equal to or somewhat greater than, the rate in control depan-

creatized dogs. This demonstrates that the inflammatory focus does not produce extra sugar.

We conclude on the basis of these experiments that the rise in blood sugar which accompanies an infection in the diabetic is not due to gluconeogenesis at the site of infection. It must be due to an increased sugar formation at the usual sites of gluconeogenesis (liver and possibly kidney).

Longevity studies of certain pathogenic bacteria on a new culture medium. RALPH MCBURNEY and LOUISE RICKEMAN CASON (introduced by E. B. Carmichael). *Dept. of Bacteriology, School of Medicine, Univ. of Alabama.* Studies of the growth of some of the more fastidious organisms which are encountered in bacteriological diagnoses have been undertaken using a splenic infusion in place of beef infusion base for the growth medium. An attempt has been made to determine the longevity of organisms on this medium.

Eleven different strains of pathogenic bacteria, consisting of streptococci, pneumococci, meningococci, gonococci, H. pertussis, C. diphtheriae, and H. influenzae were used in the experiment.

Inoculations were made on various types of media consisting of splenic infusion agar with and without Vitamin B<sub>1</sub> and splenic infusion gelatin with and without Vitamin B<sub>1</sub>. At the same time inoculations on beef infusion agar with Vitamin B<sub>1</sub> and beef infusion gelatin with varying amounts of gelatin both with and without Vitamin B<sub>1</sub> were made.

Monthly transfers from the original inoculations were made over a period of a year. Hemolytic and anhemolytic streptococci, pneumococci, and C. diphtheriae on splenic media were found to be alive for six months up to a year, which was considerably longer than on beef infusion media.

Splenic medium was not conducive to the growth of H. pertussis or H. influenzae. However growth of meningococci and gonococci was most luxuriant on the splenic medium and both strains remained alive six weeks on this. Streptococcus viridans did not survive as long on the splenic medium as on the beef infusion medium.

In as much as the growth of all strains was so profuse, it is deemed advisable to use splenic infusion media for carrying stock cultures of the organisms investigated, other than H. pertussis and H. influenzae, over long periods.

Blood pressure effects of renin and of changes in intracranial pressure following decerebration and cord section. ROBERT H. McCARTER (by invitation), M. H. F. FRIEDMAN and FRANCIS M. FORSTER (by invitation). *Depts. of Physiology and Neurology, Jefferson Medical College, Philadelphia.* The effects on blood pressure produced by intravenous administration of renin and by increasing the intracranial pressure above the blood pressure level were studied in normal and acutely decere-

brated cats and in cats with acute and chronic section of the lower cervical and upper thoracic spinal cord. In the normal and decerebrate animal and animal with chronic section of the cord, administration of renin always produced a definite increase in blood pressure. However, when acute section of the cord resulted in a sustained depression in blood pressure to shock levels renin alone was not effective, but adrenaline administered immediately after renin produced a greater and more prolonged rise in blood pressure than could be expected from adrenaline alone. Elevation of the intracranial pressure during the height of the renin rise caused a still further rise in blood pressure. In animals with acute section of the low cervical or high thoracic cords elevation of the intracranial pressure resulted in only a slight to moderate increase in blood pressure whereas in animals with chronic cord sections the increase was more pronounced.

The effect of acetate and tension on the motor activity of the isolated small intestine. J. F. MCCLENDON. *Hahnemann Medical College, Philadelphia.* Replacement of 25% of Ringer's fluid with 0.2 N sodium acetate (at pH 7.4, with 1 ion of Ca to 100 Na) stimulated the amplitude of the rhythmic contractions of both longitudinal and circular muscle of the rabbit or rat gut. The circular muscle was recorded by inserting 2 "keyrings" into a short segment of gut. Since injecting acetate into the lumen might distend the gut and since moderate distention stimulates motor activity, the gut was turned inside out for the acetate to act on the mucosal side.

Turning the gut inside out abolishes motor activity as measured longitudinally. This is apparently due to relief of circular tension on the peritoneal and longitudinal muscle portion of the wall. If a segment of gut is cut longitudinally it partially turns itself inside out and there is a corresponding depression of motor activity. If a normal segment and an inside-out segment are cut longitudinally the motor activity returns to the level before cutting. This shows that the effect of turning inside out or cutting is not due to loss of intestinal contents. Furthermore, cleaning out the intestinal contents with a pipe cleaner has no effect on the motor activity. Attaching a piece of gut to a tube and introducing acetate through the tube stimulated motor activity before it had time to flow out the other end and thus reach the peritoneal surface.

Prevention of dental caries with fluorapatite II. J. F. MCCLENDON and WM. C. FOSTER (by invitation). *Hahnemann Medical College, Philadelphia.* For 3 years, daily, we have been brushing the molar teeth of a succession of litters of rats with fluorapatite (litter-mate controls on the same diet being unbrushed. Fed. Proc. 2:34, 1943). Rats with teeth

brushed daily with fluorapatite for 60-100 days from weaning averaged 0.16 carious teeth per rat, whereas litter-mate controls averaged 3 carious teeth per rat. Rats with teeth brushed 100-150 days averaged 0.6 carious teeth per rat whereas litter mate controls averaged 4 carious teeth per rat.

The teeth of 120 medical students were examined for dental caries at the beginning and end of a one year period by Aris Carpousis, D.D.S. Of these, 40 were given fluorapatite to brush their teeth and 80 were used as controls. The 40 developed an average of 0.5 new caries per man and the 80 controls developed an average of 1.5 new caries per man. Since the fluorapatite was nearly 4% fluorine and tooth powder might be swallowed, one of us swallowed 1 gram daily for 3 years. No effect on the bones has been detected but we issued a warning that such quantities may mottle the teeth of children under 8 years. We have shown that fluorine is absorbed from fluorapatite by plant roots and similarly we presume that some exchange may take place with the tooth surface. If the fluorapatite is swallowed, some fluoride may be secreted in the saliva.

**Antidiuretic substance in the supraoptic nucleus of the dog.** ELEANOR V. MELVILLE (by invitation) and KENDRICK HARE. *Dept. of Physiology, State Univ. of Iowa, Iowa City.* Antidiuretic assays of acetic acid extracts of the neurohypophysis, hypothalamus and cerebral cortex show a graded potency of the following order: neurohypophysis, 750 mu/mgm.; hypothalamus, 1.5 mu/mgm.; and cortex, 0 mu/25 mgm. of fresh tissue. Practically all the antidiuretic material in the hypothalamus was localized in the region of the supraoptic nucleus. This tissue contained about 15 mu/mgm. Degeneration of the supraoptic nucleus following stalk section or hypophysectomy is attended by a diminution in antidiuretic potency. In these cases the antidiuretic activity varied from 1 to 20% of normal.

**Results of applying tetanus toxin to monkey's cerebral cortex.** FRED A. METTLEN and THOMAS J. PUTNAM (by invitation). (Aided by grant from Wm. J. Matheson Commission.) *Dept. of Neurology, College of Physicians and Surgeons, Columbia Univ., New York.* In order to determine whether tetanus toxin might be profitably employed as a subacute, stimulating agent, for purposes of neurophysiologic research, unpreserved toxin (courtesy of Lederle Laboratories) was applied to area 4 of one side of the monkey's cortex cerebri. Application was done under usual surgical technique and by applying (for 5 minutes) a 2 mm. square of Whatman #1 filter paper, soaked in toxin, to the leg area.

With lethal doses, generalized signs came on within three days and without evidence of any

difference between the sides of the body. With sublethal doses, capable of producing symptoms, unremitting trismus and spasmoid, bilateral elevation of the bulbi always occurred. No paralyses nor restrictions of movement of the trunk nor extremities were present but contralateral, clonic spasms of the leg occurred at very wide intervals and in an unpredictable manner. They could not be deliberately induced. The patellar reflex of the affected extremity showed a higher threshold, narrower reflexogenous zone, looser quality and lower amplitude than its fellow. Both plantar responses were of a flexor nature.

Although the evidence at hand suggests a localized action, beginning at the site of application, the cortical application of toxin evidently results in symptoms of a less restricted nature than those which follow intraspinal application or intramuscular injection of an extremity.

**Effect of an extract of hog's stomach and duodenum on utilization of tocopherol in progressive muscular dystrophy.** A. T. MILHORAT. *Depts. of Medicine and Psychiatry, Cornell Univ. Medical College, The Russell Sage Inst. of Pathology and The New York Hospital, New York.* Recent studies<sup>1</sup> have shown that oral administration of tocopherol that previously had been incubated in the stomach of a normal man can reduce the creatinuria of patients with progressive muscular dystrophy, whereas the untreated vitamin is without effect. In the present investigations an extract of hog stomach and duodenum was given to 6 patients one-half hour after meals for periods of from 3 to 7 days. No tocopherol in addition to that contained in the normal diet was given. Aside from a temporary rise in creatine output (due to creatine in the extract) no effect on creatinuria was observed in 5 of the patients. In the 6th subject, questionable effects on creatinuria were observed during the 7 days when the extract was given. However, when the administration of the extract was discontinued, the creatine output was immediately reduced. By the third day the creatinuria had decreased to one-half of the previous control level. The output of creatine remained at this low level for 3 days, and then gradually increased, reaching the previous control level in about 12 days.

**Determination of plasma volume changes after hemorrhage by the dye method.** A. T. MILLER, JR. *Dept. of Physiology, Univ. of North Carolina Medical School, Chapel Hill.* The apparent simplicity of the dye method for determining plasma volume has led to its non-critical use in studies on shock and hemorrhage. The following procedure eliminates certain sources of error. (1) A reference dye-disappearance curve (using the blue dye T-1824) is constructed for each animal from the

<sup>1</sup> Milhorat, A. T. and W. E. Bartle, *Science* 101: 53, 1945.

average of 2 or more curves determined 1 week apart. This curve, plotted on semi-log paper, closely approximates a straight line for periods up to 6 hours. The slope of this reference curve is constant for a given animal over periods of many months. (2) On the morning of an experiment, the position of the curve is checked by injecting dye and determining dye concentration at intervals of 20, 40 and 60 minutes. (3) The animal is hemorrhaged rapidly from a femoral artery. (4) Blood samples are taken at desired intervals, depending on the phase of fluid restoration being studied. (5) Plasma volumes at these sampling times ( $PV_H$ ) are calculated from the formula  $PV_H = D_s/D_H PVR$ , where  $D_H$  = dye concentration on the reference disappearance curve at the corresponding time and  $PVR$  = reduced plasma volume (initial plasma volume minus volume of plasma withdrawn by hemorrhage). (6) At the conclusion of the experiment the animal is transfused with citrated blood and may be used for another experiment after 2 days.

This procedure provides a standardized animal for assay of the influence of accessory factors (heat, cold, anesthesia, etc.) on the rate of plasma volume restoration after acute hemorrhage.

**Environmental heat gain of man in hot humid climate.** G. W. MOLNAR, E. J. TOWBIN and A. H. BROWN (introduced by E. F. Adolph). *Dept. of Physiology, School of Medicine and Dentistry, Univ. of Rochester, Rochester, N. Y.* The influx of heat from the environment (including sun) was determined in Florida during August. The range of climate was: dry bulb, 75-91°F.; relative humidity, 60-83%; wind, 35-775 ft./minute; sun, 528-888 Cal./m.<sup>2</sup> normal incidence hr. and shade. The heat gain was taken to be the difference between evaporative heat loss and heat production  $\pm$  storage. The prevailing temperature range for any one series of observations was too small to disclose a correlation between air temperature and heat gain. A total of 48 determinations (storage assumed to be zero in 9) on four sitting men, clothed or in shorts and shoes, in or out of the sun (shade, shelter, night), show that environmental heat gain varies linearly with rate of sweat loss. Heat gain was negative below a sweat loss of 125-150 gm./hr.; positive above this value. Empirically, 100 grams/hr. of sweat loss was equivalent to 57.8 Cal./hr. of heat gain.

Positive heat gain occurred only in the sun (dry bulb 87°F. or lower), and at a rate linear to the solar intensity. The gain became positive for the nude man at one-half maximal solar intensity; for the clothed man at two-thirds maximal intensity. The heat gain increased by about 30 Cal./hr. per man for each rise in solar intensity of 60 Cal./m.<sup>2</sup> normal incidence/hr. At maximal solar intensity, the nude man gained about 200 Cal./hr., a gain

equal to that in the desert at the same temperature. Clothing diminished the solar heat gain by 40-80 Cal./hr./man at any given solar intensity.

*Work done under contract with the Office of Scientific Research and Development. Field studies were made possible by various units of the U. S. Army.*

The physiological factors which govern inert gas exchange.<sup>1</sup> Lt. (jg) M. F. MORALES and Lt. R. E. SMITH, USNR (introduced by H. R. Catchpole). *Naval Medical Research Inst., Bethesda, Md.* A quantitative theory of inert gas exchange by a tissue region or by the whole body has been developed and found to agree with experiment. The rate of exchange is governed by decay constants which are known functions of rate of blood flow, volume of blood and extracellular fluid, blood-cell partition coefficient, cell permeability, total cell volume, and the ratio of capillary surface to gross volume of tissue. This dependence permits quantitative prediction of variations in the rate of exchange attending any given changes in the physiological state. Also discussed are the implications which the results have for selection and therapeutic problems associated with decompression sickness.

An evaluation of the effect of stasis in the production of experimental thrombosis. CAMPBELL MOSES (introduced by C. C. Guthrie). *Dept. of Physiology and Pharmacology of the School of Medicine of the Univ. of Pittsburgh.* In an attempt to develop a method for consistently producing experimental thrombosis the effect of sclerosing agents and the insertion of various intravascular foreign bodies in the presence and absence of stasis is described. A method is given for consistently producing occluding red thrombi by the insertion of wool yarn impregnated with defibrinated blood into a vein and slowing blood flow in the vessel by a metal clip. The importance of the stasis and congestion thereby produced in the consistent production of experimental thrombosis by this method is emphasized.

The effect of heparin and dicoumarol on thrombosis induced in the presence of venous stasis. CAMPBELL MOSES (introduced by C. C. Guthrie). *Dept. of Physiology and Pharmacology of the School of Medicine of the Univ. of Pittsburgh.* Using rabbits as the experimental animal and a method capable of inducing thrombosis in all control animals, the effect of heparin and dicoumarol in delaying or preventing thrombosis was studied. The administration of these drugs in doses adequate to delay coagulation did not prevent the development of experimental intravascular thrombosis in the presence of stasis in the venous circulation. In the absence of stasis heparin and

<sup>1</sup> The opinions expressed in this article are those of the writers, and are not to be construed as reflecting the official views of the Navy Department or of the naval service at large.

dicoumarol [3,3'-methylenebis(4-hydroxycoumarin)] might retard but did not prevent the development of experimental intravascular thrombi. The results emphasized the important rôle of stasis in the pathogenesis of thrombosis.

**Effect of various marine oil preparations on experimental renal hypertension.** W. G. Moss (by invitation) and G. E. WAKERLIN. *Dept. of Physiology, Univ. of Illinois College of Medicine, Chicago.* We have previously reported the effect of various vitamin preparations on experimental hypertension in the dog (Fed. Proc. 3: 34, 1944). These observations indicated that some vitamin A concentrates had an antihypertensive effect when administered orally which was not due to the vitamin. Having extended this study we now report our results using a number of fish liver and body oils (containing 200,000 units of vitamin A per cc.) and residues from the distillation of such oils (containing little or no vitamin A).

Nine preparations of marine fish liver oils containing vitamin A have been assayed orally in experimental hypertensive dogs in a dose of 2 cc. per day for 4 to 6 months. One of these oils showed excellent blood pressure reducing properties, two gave slight reductions, and the others were ineffective.

A residue oil obtained from the preparation of vitamin A concentrates (in a daily dose of 2 cc.) and a residue obtained following the distillation of fatty acids from mixed fish body oils (in a daily oral dose of 6 gms) were assayed each on one hypertensive dog for 4 months without any antihypertensive effect. Another residue from marine fish liver and body oils assayed orally in a dose of 6 gms per day for 4 months produced a good reduction in blood pressure which, however, was not sustained even by doubling the dose.

An orally effective antihypertensive agent of unknown identity appears to be inconstantly present in marine fish liver and body oils and fractions thereof. [This work was aided by a grant from the Winthrop Chemical Company.]

**The electrophoretic components of canine pancreatic juice.** MURIEL PLATT MUNRO (by invitation) and J. E. THOMAS. *The Charlotte Drake Cardeza Foundation, Dept. of Medicine, and the Dept. of Physiology, Jefferson Medical College, Philadelphia.* Using a method described elsewhere in this issue (Hart and Thomas) pure, inactive pancreatic juice was collected through sterile tubes into an iced flask, from three chronic duodenal fistula dogs. Secretion was evoked by means of neutral peptone, soap or acid peptone injected into the intestine.

The samples of juice were studied in the Tiselius electrophoresis apparatus after dialysis against sodium bicarbonate-sodium chloride buffer at pH 8.2. Exposure of the pancreatic juice to the voltage

required for fractionation over a period of four hours caused no activation of the trypsin and no reduction in the tryptic activity after activation with enterokinase. The electrophoretic patterns show that pancreatic juice contains five different protein constituents whose mobilities and relative concentrations are independent of the stimulus, and of the total nitrogen content of the juice. The average mobilities of the five components as obtained in seven experiments involving two dogs and the three stimuli were 5.4, 4.1, 2.8, 1.7, and  $0.7 \times 10^{-5}$  cm./volt/cm./sec. The juice from the third dogs also had five constituents which differed from those of the other two dogs in that the fastest-moving constituent was absent and a new one having a mobility of  $1.2 \times 10^{-5}$  was present. A comparison of these mobilities with those of the protein fractions of dog plasma indicate that the second and third fractions have the same mobilities as  $\alpha_2$ - and  $\beta$ -globulins respectively. Whether these pancreatic fractions are identical to plasma globulins has not been established, but the similarity in mobility suggests such a possibility.

**Hypothalamic facilitation of the motor cortex.** J. P. MURPHY (by invitation) and E. GELHORN. *Laby. of Neurophysiology, Dept. of Physiology, Univ. of Minnesota.* The effect of simultaneous stimulation of the hypothalamus upon stimulation of the motor cortex was studied in the cat. Over 350 experiments were performed on 20 animals.

Hypothalamic stimulation (bipolar) was effected by a Harvard inductorium, 3V primary, secondary coil at a distance productive of sympathetic phenomena (contraction of the nictitating membrane and maximal pupillary dilatation) from the posterior nuclei without motor movements. Cortical stimulation (bipolar) was induced by condenser discharges with intensity of voltage at threshold or slightly above. The results of the latter were then compared with those produced by stimulation of both hypothalamus and cortex together.

It was found that stimulation of the posterior hypothalamic and adjacent nuclei facilitates the motor cortex. This is expressed as shortening of latency of motor response, intensification of movements, spread of movements, or combinations of all three. The facilitatory effect is as pronounced on the contralateral as on the ipsilateral cortex. It persists after bilateral cervical sympathectomy and after transection of the medulla. No facilitation of the cortex results from stimulation of anterior hypothalamic nuclei which do not cause sympathetic discharges.

It appears most probable that activation of the posterior, sympathetic hypothalamus results in discharge of the thalamo-cortical system described by Morison, Dempsey, and collaborators. It is suggested that initiation or accentuation of motor

phenomena during emotional states may have a basis in hypothalamic-cortical facilitation.

**On the chemical mechanism of nervous action.** DAVID NACHMANSOHN. *Dept. of Neurology, College of Physicians and Surgeons, Columbia Univ., N. Y.* Recent investigations have provided evidence for the assumption that the release and the removal of acetylcholine are *intracellular* processes directly connected with the nerve action potential at points along the neuronal surface. The ester released by a stimulus depolarizes the membrane by rendering it permeable to all ions. Thus, flow of current is generated (action potential) which stimulates the adjacent region. There the process is repeated, and the impulse in this way propagated along the axon. At the nerve ending, owing to the increased surface, there is less resistance and more flow of current enabling the impulse to cross the non-conducting gap.

The concept is mainly based on studies of cholinesterase. Three essential features are: (1) the high concentration of the enzyme in nerves making possible a rate of acetylcholine metabolism parallel to that of the electric changes; (2) the localization of the enzyme at the neuronal surface, and (3) the parallelism between enzyme activity and voltage of the action potential.

The energy released by phosphocreatine breakdown is adequate to account for the electric energy released by the nerve action potential. Hence if the release of acetylcholine is the primary event responsible for the alterations of the nerve membrane during the passage of the impulse, phosphate bonds should be used for acetylcholine synthesis.

In accordance with this hypothesis a new enzyme, choline acetylase, has been extracted from brain which in presence of adenosinetriphosphate under anaerobic conditions and in cell-free solution synthesizes acetylcholine.

**The influence of glucose on gastric emptying.** DAVID W. NORTHUP and EDWARD J. VAN LIERE. *Dept. of Physiology, School of Medicine, West Virginia Univ., Morgantown.* The effect of glucose on gastric emptying in man was studied. The glucose was added in different amounts to a standard test meal. Eighteen young adults served as subjects. The test meal was prepared by boiling 15 gm. of farina in water to a volume of 200 cc.; 100 gm. of BaSO<sub>4</sub> was added to visualize the meal fluoroscopically. When glucose was added it was dissolved in the meal at the time of its preparation.

The average emptying time for the group with the standard meal alone was 2.23 hours; with 25 gm. of added glucose, 2.76 hours; with 50 gm., 3.09 hours; with 75 gm., 3.36 hours. The results are statistically significant.

The delay in gastric emptying is roughly proportional to the concentration of glucose in the meal.

**Respiration in elasmobranch fishes.** ERIC OGREN. *Dept. of Physiology, School of Medicine, Univ. of Texas, Galveston.* Two-foot specimens of *Murdoch californicus* were placed in a small tank with their heads through a rubber diaphragm which effectively separated the water entering their mouths and gills from that leaving their gills. The frequency of respiratory movements increased with temperature and diminished with chloroform anesthesia or with excitement or activity. In apparently normal conditions the fish pumped from one to one and one-half liters per kilogram per minute and the amount was increased by increasing the pressure on the inspiratory side relative to the expiratory side and vice versa. Changes on the O<sub>2</sub>, CO<sub>2</sub>, and non-volatile acid content were without effect on the respiratory flow or frequency up to the limit of the fishes' tolerance. When artificially lowered flow or chemical changes in the inspired water brought the pH of the expired water below 7.0 the fish would react with generalized struggling. When the inspired water approached pH 7.0 the expired water had a higher pH than that taken in. The struggling response to respiratory insufficiency by violent rhythmic contraction of the segmented muscles which are locomotor in function may bear an interesting relationship to the reaction of the diaphragm, thoracic, and abdominal muscles in mammals whose locomotor functions tend to be vestigial and whose respiratory functions are well developed. [Experiments done at the Scripps Institution of Oceanography, LaJolla, California, by courtesy of Dr. Harald U. Sverdrup, director, and Dr. F. B. Sumner.]

**The apparent nervous factor in experimental shock.<sup>1</sup>** R. R. OVERMAN (by invitation) and S. C. WANG. *Dept. of Physiology, College of Physicians and Surgeons, Columbia Univ.* Thirty experiments with sublethal hemorrhage coupled with electrical stimulation of the central cut-end of both sciatic nerves have been completed. It was found that such dogs rarely survived with a residual circulating blood volume of less than 67 cc. per kilogram body weight, compared with 58 cc. per kilogram in animals suffering from simple hemorrhage. The residual blood volume at L. H. 50 in this series (lethal hemorrhage at 50 per cent mortality) is calculated to be 66 cc. per kilogram. This value is significantly different from that in simple hemorrhage (57 cc. per kilogram). In other words, the mortality rate in hemorrhage is definitely increased by additional afferent stimulation. Animals in the stimulation series not only presented clinical manifestations similar to those receiving muscle trauma but also succumbed suddenly when the level of the mean blood pressure was relatively high (60 mm. Hg or higher).

<sup>1</sup> This work was done under a contract, recommended by the Committee on Medical Research, between the Office of Scientific Research and Development and Columbia University.

Our studies of the afferent nervous factor in experimental traumatic shock are yet to be completed with a series of trauma experiments, in which the hindlegs have been previously deafferented in order to see if such animals may survive with a smaller residual blood volume than normal animals subjected to muscle trauma. In 10 such experiments thus far completed the clinical manifestations were very similar to those observed after simple hemorrhage.

The fluorescein circulation time in experimental traumatic shock.<sup>1</sup> E. E. PAINTER, S. C. WANG and R. R. OVERMAN (by invitation). *Dept. of Physiology, College of Physicians and Surgeons, Columbia Univ.* Repeated determinations of circulation time by Fishback's fluorescein method were made on 32 dogs. Normal circulation time ranges from 9 to 16 seconds. In traumatic shock the circulation time is invariably prolonged. For the prognosis of the traumatized animal two determinations, separated by one hour's interval, are essential. If the second circulation time is longer than the first and more than 30 seconds, the dog will not survive. On the other hand, if the circulation time is less than 25 seconds or considerably shorter than the first, prognosis is good. The change in circulation time is an early index of eventual recovery or death; this is significant at a time when the blood pressure and heart rate remain unchanged for several hours.

After trauma, five dogs in which both upper thoracic chains had previously been removed, showed a plateau of circulation time of 20 to 30 seconds for several hours followed by an abrupt rise shortly before death. In 3 normal dogs circulation times by both the cyanide and fluorescein methods were simultaneously determined. The cyanide circulation time, although increased, remained at a fairly constant level (as does the fluorescein circulation time in ganglionectomized animals) while the fluorescein circulation time showed progressive changes over the same period. This indicates that in normal animals which succumbed from trauma there is a progressive increase of vaso-constriction in the peripheral capillaries which was included in the measurement of circulation time by the fluorescein but not by the cyanide method.

Influence of thiouracil on the oxydase content of the thyroid gland. K. E. PASCHIKS, A. CANTAROW, A. E. RAKOFF (by invitation) and E. K. TULLSON (by invitation). *Jefferson Medical College and Hospital, Philadelphia.* Oxydase content of thyroid glands of rats was determined by a modification of the colorimetric method of Galli-Mainini.

The oxydase activity of thyroid glands was decreased by adding thiouracil *in vitro*. Thyroid glands from rats treated with thiouracil for periods of 5 days to 4 weeks showed a lower oxydase activity per unit weight of the gland than did thyroids of untreated controls. This is all the more significant since the cell volume of the thyroid gland of treated animals is much greater than that of normal glands.

Since it is believed that cytochrome oxydase is essential for synthesis of thyroxin our experiments indicate that inhibition of oxydase may be a factor in the suppression of thyroid function through thiouracil.

The rôle of the proprioceptors in shivering. JOHN F. PERKINS, JR. (introduced by Hallowell Davis). *Dept. of Physiology, Harvard Medical School, Boston, Mass.* Shivering in cats was recorded by means of two phonograph pickups connected to a two-channel ink-writing oscillograph. Motion was imparted to each pickup by a moderately stiff wire, substituted for the phonograph needle, resting against a limb, or connected to a tendon detached from its insertion. Shivering was recorded simultaneously in normal and deafferented hind limbs and in pairs of muscles of such limbs. The tremor was rhythmic on the normal side, but was always irregular on the deafferented side. A hemi-decerebellate animal, and two animals with severance of one dorsal column shivered normally.

The rate of shivering in a normal muscle could be varied by as much as 100 per cent by varying the mechanical period of the moving parts. The tendon pulled vertically against a rubber band. One end of a light lever, 15 cm. long, was also attached to the tendon. Equal weights were mounted at equal distances from the fulcrum. The rate of tremor increased when the weights were set closer together, or when tension of the rubber band was increased. In normal animals, the rates in corresponding muscles could be varied independently. Deafferented muscles did not shiver rhythmically even with this arrangement.

It is concluded that the rhythmicity of shivering is determined peripherally by a mechanism involving the proprioceptors and resembling that of reflex clonus. The rate is probably close to the resonant frequency of the moving part. A pacemaker action of the shivering center appears unlikely.

Effects of high acceleratory forces. V. A. PRETZTORF (by invitation) and S. W. BRITTON. *Dept. of Physiology, Univ. of Virginia Medical School, Charlottesville.* Responses of monkeys, dogs, cats, rats and other animals to high acceleration (centrifugation) have been studied over the past four years. In most cases forces up to 6 gram have been

<sup>1</sup> This work was done under a contract, recommended by the Committee on Medical Research, between the Office of Scientific Research and Development and Columbia University.

considered; in some instances, however, tests at 50 gram were also observed in a few experiments.

Respiration, pulse, blood pressure and flow, E.C.G. and E.E.G. changes have been specially studied. Other circulatory conditions, blood glucose and electrolytes, and skin resistance were also noted under acceleratory stresses.

The effects of protective devices, belts and bandages, various gases, vasopressors, etc., have also been determined.

**The nature of the renal tubular mechanism for acidifying the urine.** R. R. PITTS and R. S. ALEXANDER (by invitation). *Cornell Univ. Medical College, N.Y.C.* Three concepts have arisen concerning the nature of the renal mechanism for acidifying the urine. 1, Dibasic phosphate is preferentially reabsorbed from the glomerular filtrate. Monobasic phosphate is excreted and acidifies the urine. 2, Carbonic acid in the glomerular filtrate transforms dibasic phosphate to monobasic phosphate within the tubular lumen. Base is reabsorbed as bicarbonate. 3, Hydrogen ions are transferred from tubule cells to tubular urine in exchange for base.

These three theories have been critically tested in dogs rendered acidotic by the daily feeding of HCl and infused with large amounts of neutral sodium phosphate. The quantities of carbonic acid and monobasic phosphate filtered through the glomeruli are sufficient to account for only 20 to 30

cent of the observed urinary acid. Since these are the only acid substances present in the glomerular filtrate in significant amounts, acidification of the urine must per force be effected by a tubular mechanism. The following tubular mechanism is suggested. Hydrogen ions formed within the renal tubule cells are exchanged for sodium ions present in the glomerular filtrate. The tubular source of hydrogen ions is carbonic acid, formed by the intracellular hydration of carbon dioxide. Renal carbonic anhydrase increases the rate of hydration of carbon dioxide, thus the rate of formation of hydrogen ions, and the rate of excretion of acid. When large amounts of sulfanilamide are infused to depress the activity of the renal carbonic anhydrase, the rate of excretion of acid diminishes.

**The effect of reticulo-endothelial immune serum (Reis) on heart fragments in tissue culture.** CHARLES M. POMERAT and LUDWIK ANIGSTEIN (by invitation). *Depts. of Anatomy and Preventive Medicine, Univ. of Texas, Medical Branch, Galveston.* Chick spleen and bone marrow were injected repeatedly into rabbits from which reticulo-endothelial immune serum (REIS) was produced. Serial dilutions of this serum were made up with extract from chicks incubated for 6 to 9 days. Heart fragments from chicks used in the preparation of the extract were cultivated in clots formed of equal parts of the fluid containing the embryonic extract

and freshly heparinized rooster plasma. Normal rabbit serum was used in the medium for control cultures. All experiments were conducted in hanging drop preparations and incubated at 37.5°C.

Total inhibition of cellular outgrowth was observed in the presence of REIS at 1/4, while at 1/400 some evidence of stimulation was noted, in comparison with controls. The complement-fixation titre of the REIS used was 1:1200. Planimeter measurements of culture outlines made with a projectoscope offer a simple method of evaluating possible stimulating action of REIS. Results obtained with heart fragments confirm previous reports on the inhibitory action of REIS at high concentration. In addition, they show an overlapping antigenic specificity with respect to the organ used. This may indicate that a dedifferentiated embryonic heart cell, mesenchymal in character, is highly sensitive to REIS.

**Reflex facilitation following muscle ischemia.** E. L. PORTER and E. L. CALLAHAN (by invitation). *Dept. of Physiology, Med. School, Univ. of Texas, Galveston.* In a previous abstract (Tex. Acad. Sci. 25: 59, 1941) we reported that in a spinal cat ischemia of the leg brought about facilitation of flexion reflex response to minimal shocks to a sensory nerve. This ischemia involved the muscle used for recording as well as the other muscles of the leg. Would this facilitation occur if the recording muscle were allowed to retain its circulation while other muscles were rendered ischemic? We have found facilitation does so occur. If the posterior tibial nerve is stimulated to cause minimal reflex response in the tibialis anticus muscle and then both posterior and anterior tibial arteries are ligated below the exit of the blood vessels to the tibialis anticus muscle the facilitation of the reflex response still occurs. The supposition is that ischemia of the muscles causes what would be pain in the conscious animal. In the spinal cat these "pain" impulses summate with the "painful" stimulation of the posterior tibial nerve to cause a higher reflex response. Possibly such reflex summation or facilitation may be involved in the pain (causalgia) following nerve injury.

**Neuro-muscular transmission following ischemia.** E. L. PORTER and A. N. TAYLOR (by invitation). *Dept. of Physiology Medical School, Univ. of Texas, Galveston.* Porter and Callahan have reported (Proc. Amer. Physiol. Soc., 2: 38, 1943) that ischemia of a muscle (cat) causes temporary improvement of contraction when the muscle is stimulated through its nerve by minimal shocks and that this result is not obtained in a curarized muscle. The method involved changing the type of stimulation from a special liquid electrode on the nerve for uncurarized muscle to needle electrodes within the muscle after it was curarized. This shifting of electrodes rendered it somewhat

uncertain as to whether the results obtained were strictly comparable.

We have confirmed the original findings by using needle electrodes inserted into the muscle throughout the experiment. The improvement of contraction still occurs following ligation of the femoral artery but does not occur after the muscle is curarized. Since with the other method it had been observed that circulation through the nerve at the point of stimulation still continued after low ligation of the femoral artery the conclusion seems justified that the improvement in contraction following ischemia is not due to an effect on the nerve trunk at the point of stimulation. And since the effect is not found in a curarized muscle the conclusion seems warranted that ischemia improves neuro-muscular transmission. Synaptic transmission in the cord appears to be temporarily improved by asphyxia. (Porter, Blair & Bohmfalk, *Jour. Neuro-Physiol.* 1: 166, 1938).

**Alteration in water content of the brain after concussion.** W. A. RAMBACH, JR. and M. ROBERT DE RAMIREZ DE ARELLANO (introduced by W. F. Windle). *Inst. of Neurology, Northwestern Univ. Medical School, Chicago.* Water content of the guinea pig's brain was determined by triple extraction with acetone, drying the acetone extract and residue separately in a vacuum over at 60°C. and comparing with the original wet weight of the tissue. Complete desiccation was effected in 26 to 29 hours. Groups of animals were selected according to sex and weight and each experimental group was paired with a similar control group. Alteration in water content of the brain was studied at 4, 8, 16 and 24 and 48 hours after concussion.

At 8 and 16 hours after concussion the water content was maximum, the rise amounting to 0.5 per cent of wet brain weight. By 24 hours it was beginning to decline and at 48 hours the values were normal. The actual mean increase amounted to 19 mg., which is about half a drop of water per brain. Results were statistically significant.

Water increase was determined after producing bilateral 1-cm. openings in the parietal skull of 9 guinea pigs. The brain was not deliberately traumatized and in most cases the dura was left intact. Twenty-four hours after this operation, a mean water increase of 0.77 per cent was demonstrated. Other animals in which the brain had been similarly exposed were killed 6 days later for histologic study. No alterations in interneurons of the brain stem comparable to those observed after concussion were found. [Work done under contract, sponsored by CMR, between OSRD and Northwestern Univ.]

**Alteration in the response to electrical stimulation of the respiratory center by picrotoxin.** M. ROBERT DE RAMIREZ DE ARELLANO, W. A. RAMBACH, JR., H. M. SCHAMP and J. RANKIN (introduced by W. F. Windle). *Inst. of Neurology, North-*

*western Univ. Medical School, Chicago.* Experiments were performed to determine effects of picrotoxin (0.4 mg. per kg., intravenously) on excitability of the respiratory center to electrical stimulation by means of electrodes implanted with the Horsley-Clarke instrument. Three types of physiological preparation were used.

(a) In intact cats anesthetized with phenobarbital (150 mg. per kg., intraperitoneally) stimulation of the respiratory center after administering picrotoxin led to a marked sustained rise in the volume of inspired air and an increase in respiratory rate. The response lasted three to six or more hours. Control experiments showed no comparable response.

(b) In cats decerebrated by the anemia technique the same dosage of picrotoxin led to a marked decrease in the response of the respiratory center to direct electrical stimulation. This was accompanied by increase in respiratory rate and decrease in tidal air. Minute volume was increased.

(c) By cross circulation, the cat's brain rostral to the middle pons was kept alive while picrotoxin was administered to the blood stream supplying parts below the middle pons. Results were comparable to those in intact barbiturized animals. When the drug was allowed to act upon the rostral parts of the brain through the donor cat's blood stream no significant changes occurred.

The estimation of cutaneous blood flow from the photoelectrically recorded cutaneous volume pulses. W. C. RANDALL, K. E. JOCHIM and A. B. HERTZMAN. *Dept. of Physiology, St. Louis Univ. School of Medicine.* Previous studies indicated that the photoelectrically recorded cutaneous volume pulses could be expressed as blood flow. Theoretical considerations and calibration data indicate that the cutaneous arterial inflow may be represented by a simple geometrical construction in which a triangular flow curve (the flow pulse) is superimposed on a rectangular base. The sum of these two areas expresses the flow during a pulse cycle; they vary together. Hence, since the area of the triangular flow pulse is proportional to its height, and since the sum of the pulse areas over a period of one minute is independent of the pulse rate (this follows from the fact that the pulse cycle times the pulse rate is constant), and if the cutaneous volume pulse mimics the flow pulse, then the cutaneous blood flow can be estimated from the equation flow equals  $K \cdot P$ , where  $P$  (amplitude of volume pulse) is expressed in "filter units" and  $K$  is the flow equivalent ( $\text{cc}/\text{cm}^2/\text{min}$ ) of the latter. Both theoretical considerations and preliminary tests indicate that variations in the pulse contour do not greatly affect the accuracy of the equation. The actual amplitude of the volume pulse in  $\text{cc}/\text{cm}^2$  is obtained from the expression  $\frac{P \cdot K}{PR \cdot K_1}$  where  $PR$

is the pulse rate and  $K_1$  a constant dependent on the pulse form but usually equal to 4. The data so obtained agree in the finger phalanx with those simultaneously obtained by mechanical plethysmographs.

**Changes in the physical structure of the long bones of mice after estrogen administration.** C. I. REED and B. P. REED (by invitation). *Dept. of Physiology, Univ. of Illinois, Chicago Colleges.* Earlier studies by x-ray diffraction have shown that the orientation of unit crystals of apatite in the long bones of rats may be disturbed in a non-specific manner in rickets, after administration of parathyroid extract and other dietary errors and that even in adult animals reorientation may occur. The femora of mice treated with various estrogenic substances show progressive deposition of apatite in the cancellae until the medullary canals are completely blocked. These deposits are wholly unorientated. The original cortices remain undisturbed until after the canals are completely blocked, after which disorientation slowly progresses from within outward. Orientation of medullary deposits has never been observed.

**The effect of electric current on gastric secretion and potential.** W. S. REHM (introduced by Hampden Lawson). *Dept. of Physiology, Univ. of Louisville School of Medicine, Louisville, Ky.* A portion of the pernóstomized dog's stomach (21 sq. cm.) was placed in a lucite chamber that contained two pairs of electrodes (similar to chamber described by author, Am. J. Physiol., 141: 537, 1944). One pair of electrodes was used for the application of current across the stomach wall and the other for the measurement of the potential difference. The rate of secretion of HCl (from titration and pH data) was measured at 10 minute intervals. Current was applied for 10 minute periods from serosa to mucosa and in the opposite direction in both the secreting and non-secreting stomach. When current (7 to 80 milliamperes) was sent from the serosa to the mucosa in the secreting stomach (histamine stimulated) there was an increase in the rate of secretion of HCl followed by a relatively rapid return to the original rate. When comparable amounts of current were applied in the opposite direction there was a decrease in the secretion of HCl followed by a much slower return to the original rate. Following this latter procedure the potential differences across the stomach was depressed and there was a close parallelism between the recovery of the potential and secretory rate. Application of current (10 to 150 milliamperes) in either direction to the non-secreting stomach did not result in the secretion of HCl.

**Determination of a cardiac ejection curve from the distensibility of the aorta, the pressure pulse contour, and pulse wave velocity.** JOHN W. REMINGTON and W. F. HAMILTON. *Dept. of Physi-*

*ology, Univ. of Ga. School of Medicine, Augusta.* Aortae of both dog and man were removed, cut serially into rings and optical records made of the relation between tension and length when tension was increased rapidly. From these relations the volume pressure curve of each ring and the pulse wave velocity in the various parts of the aorta were calculated. These velocities in dogs agreed with measured velocities. The pressure pulse was then divided into 10 m sec. intervals and, allowing for the transmission times to each aortic segment, the uptake of each segment per unit time was calculated and summated to give the aortic uptake curve.

Ventricular ejection supplies blood not only to satisfy the aortic uptake curve but also to compensate for drainage from each segment of the aorta. Since diastolic drainage is equal to aortic uptake and since it is proportional to pressure—20 mm. Hg., figures for drainage during each interval of systole could be approximated and added to the aortic uptake curve to make a cardiac ejection curve.

The contour of the pressure pulse accompanying one of the classical Wiggers-Katz cardiometer curves was treated in the above fashion. The resulting curve agreed closely with the cardiometer curve. Ejection curves were derived from pressure pulses taken under various physiological conditions in both dogs and men. Such curves showed characteristics which differ widely and which will be discussed individually.

**Pharmacologic actions of some benzofuranone derivatives.** R. K. RICHARDS, G. M. EVERETT (by invitation) and K. KUETER (by invitation). *Dept. of Pharmacology, Abbott Laboratories, North Chicago, Ill.* A series of benzofuranone derivatives were investigated for their pharmacologic actions, particularly their possible usefulness as antispasmodic drugs. One of the most promising of this series was 3-(Beta-diethylaminoethyl)-3-phenyl-2-benzofuranone HCl (AP 43). The LD<sub>50</sub> i.p. in mice was found to be approximately 200 mg./kg. On the isolated rabbit intestine this compound proved about  $\frac{1}{6}$  to  $\frac{1}{5}$  as active as atropine in relaxing acetylcholine-induced spasm and about one and one-half to twice as active as papaverine against barium chloride spasm. Studies on various in situ preparations and fistula dogs substantiated the marked effectiveness of this compound against several types of spasm of the digestive tract. Antagonism against histamine effects was demonstrated by different methods. Marked bronchio-dilator effect against histamine-induced spasm in the perfused guinea pig lung was observed. The atropine-like actions of AP 43 upon salivary secretion, circulatory responses, and the pupil were relatively slight. It possesses also a remarkable local anesthetic effect.

Substitution of the 3-phenyl ring by cyclohexyl

(AP 73) produces relatively little change in toxicity and pharmacologic properties. The methohbromide (AP 124) derivative of AP 43 possesses a considerably higher toxicity, its atropine-like action is greatly enhanced while the papaverine-type activity is lowered.

A direct method for the determination of carbon dioxide and oxygen tensions in blood.<sup>1</sup> R. L. RILEY (introduced by C. L. Gemmill), *School of Aviation Medicine, Naval Air Training Bases, Pensacola, Fla.* The method depends upon equilibration of a bubble of alveolar air with blood at 37°C. and analysis of the bubble for carbon dioxide and oxygen. The Roughton-Scholander syringe (*J. Bio. Chem.*, 148: 541, 193) is used both as equilibration chamber and bubble analyser, thus eliminating the necessity for transfer of the bubble. At sea level, the accuracy of this technic was tested by comparison of results with those of a tonometer method. Results agreed within 3 mm. Hg in 30 out of 38 cases for carbon dioxide and in 28 out of 38 cases for oxygen. In no instance did the difference in findings exceed 7 mm. Hg. At simulated altitudes of 9,000 to 15,000 feet the accuracy of the technic was evaluated by comparing arterial tensions with alveolar tensions. The agreement was good. The agreement was equally good between determined oxygen and carbon dioxide tensions in arterial blood and average alveolar tensions found by Boothby at equivalent altitudes.

For 18 determinations on arterial blood from resting man at sea level, carbon dioxide tensions varied between 32 and 41 mm. Hg (average 38 mm. Hg), and oxygen tensions varied between 93 and 110 mm. Hg (average 100 mm. Hg).

**Studies on the nervous control of the guinea-pig heart.** JANE SANDS ROBB, *Dcpt. of Pharmacology, Syracuse Univ., Syracuse, N. Y.* Guinea pigs anesthetized with pentobarbital, followed by nerve dissection and insertion of a tracheal cannula, some with and some without exposure of the heart have been studied. When simultaneous ECG's are recorded before, during, and after vagal stimulation, not only is the major effect ventricular, but the "escaped" beats tend to be of a "right" or "left" type, according to the side stimulated. Following physostigmine the ventricular rate is further slowed, but this can be prevented by atropine. If acetylbetamethylcholine in physiological dilutions is applied to the surface of the ventricle, on very small pads, the S-T segment is displaced. This effect is proportional to the concentration and the area involved. The S-T displacement is accentuated by physostigmine and is prevented by atropine.

These changes occur within one minute and begin to wear off after two minutes, suggesting local cholinesterase action. Acetylcholine presumably alters the electrocardiogram by preventing the depolarization of cell membranes whereas KCl in sufficient concentration is said to produce a depolarization of membranes.

If small pads moistened with 1-1000 solution of epinephrine are placed on the ventricular surface showers of premature beats occur, the contour varying with the site of application. The auricular pacemaker remains unchanged although the ventricular rate may be doubled. Similar pads placed on the auricles result in a new pacemaker and an auricular tachycardia. During vagal stimulation the S-A node temporarily regains control.

The total base of blood serum by the cation-adsorbing resin method. H. W. ROBINSON (by invitation), E. M. GNEISNEIMER and M. J. OPPENHEIMER, *Temple Univ. School of Medicine, Philadelphia.* In an acid-base balance study on 27 men and 7 women who were medical students or members of the Faculty, the total base was determined by the resin (Amberlite-IR100) method developed by Polis and Reinhold (*J.B.C.* 156: 231, 1944) and modified slightly by one of us (H.W.R.). The resin was supplied by the Resinous Products and Chemical Co. of Philadelphia. The values in the serum ranged from 148 to 165 milli-equivs., with an average of 157. This method is relatively dependable and its simplicity has much in its favor. We believe that this variation of the values of total base must be accepted for young healthy subjects with a normal acid-base condition, as the variations in pH, carbon dioxide content and chloride of the serum obtained at the same time cover the accepted variations reported in the literature.

The pH of the group ranged from 7.30 to 7.43 with an average of 7.37. These determinations were done by glass electrode (38°C.) in a cell which permitted only minimal exposure to air. The range of carbon dioxide content was 61 to 74 volumes per cent, with an average of 66. The chloride range was 88 to 105 milli-equivs. with an average of 100.

Blood was drawn under oil immediately before or after breakfast.

**Recurrence of decompression sickness on re-ascent to high altitude.** S. ROBBARD, 1st Lt., AC. *Altitude Training Unit Kingman Army Air Field, Kingman, Ariz.* The incidence of recurrence of decompression sickness in subjects who had recently experienced these symptoms was found to depend primarily upon the time spent at ground level between flights. After variable periods at ground level, the subjects re-ascented to 38,000 feet simulated altitude for 5 minutes to determine the likelihood of immediate recurrence of symp-

<sup>1</sup> The opinions or assertions contained herein are the private ones of the writer and are not to be construed as official or reflecting the views of the Navy Department or the naval service at large.

toms in the same anatomical site involved on the first flight.

Time between flights	Number of subjects	Number with recurrence of bends	% with recurrence of bends
min.			
0- 20	5	5	100
21- 60	52	26	50
61-120	52	27	52
121-180	13	5	38
181-1800	27	0	0

Average time for onset of bends on the first flight was 28 minutes, while time for recurrence averaged 2 minutes.

Of 17 subjects who had chokes on the first flight, only one had a recurrence on the second flight.

The rapid recurrence of bends on the second flight as compared with the time for its appearance on the first flight suggests that a residue frequently remains in the site in which bends occurred. This residue manifests itself on the second flight by the almost immediate recrudescence of bends pain. After 180 minutes at ground level, this residuary factor is dissipated.

**Body size and amount of oxygen used in work simulating operation of an airplane.** CORPORAL R. R. RONKIN, Med Dept. (by invitation) and PETER V. KARPOVICH, AAF School of Aviation Medicine, Randolph Field, Texas. The subjects were 27 enlisted men in the basal state, ranging from 60.5 to 75.2 inches in height and from 120 to 220 pounds. They performed standard work on a special ergometer, built as a cockpit. The subjects operated a rudder bar and a stick, and moved the trunk back, forth, and sidewise. Expired air was collected in separate Douglas bags during the arm, leg, and trunk movements and was analyzed by the Haldane method. The efficiency of the arms and legs varied from 3 to 9%. No relation between the size of the body and the efficiency of the arms could be observed, though the smaller men had greater leg efficiency. Efficiency increased with increase of load. The largest man eligible for flying training consumed 57.9% more oxygen at rest than the smallest. During work the largest man consumed 62.8% more oxygen than the smallest. The coefficient of correlation between the gross oxygen consumption and the body surface was +0.76 at rest and +0.82 at work.

**Simultaneous measurement of blood volume with dye (T-1824) and with carbon monoxide (improved method).**<sup>1</sup> W. S. ROOT, F. J. W. ROUGHTON (by invitation) and M. I. GREGERSEN, Dept. of Physiology, College of Physicians and Surgeons,

*Columbia Univ.* We have done 34 experiments on 25 dogs and 15 experiments on 10 men. The CO was administered either in the form of CO saturated blood or by CO inhalation. With the latter method the amount absorbed was determined precisely as the difference between the amount administered in the inspired air and the amount collected in the expired air during and following the inhalation. The results are expressed in the table as the ratio of the true blood volume (plasma volume with T-1824 + total erythrocyte volume determined with CO, assuming no rapid combination with myoglobin) to the blood volume estimated with the dye method ( $\frac{\text{plasma volume}}{1 - \text{hematoerit}}$ ). The agreement between the two methods suggests that the unequal distribution of erythrocytes in the circulation is not as great as hitherto believed and that the total blood volume as determined with T-1824 is essentially correct.

*Summary of blood volume measurements with CO and with dye (T-1824)*

Subject	No. of experiments	Ratio $\frac{\text{TBV (dye)}}{\text{True TBV}}$	
		Range	Average
Normal dogs.....	7	0.93-1.04	0.99
Splenectomized dogs.....	16	0.97-1.07	1.03
Hemorrhaged dogs.....	5	0.88-1.01	0.97
Traumatized dogs.....	6	0.94-1.00	1.00
Normal man rest.....	11	0.98-1.05	1.01
Normal man work*.....	3	0.99-1.02	1.01

\* The work was carried out under tropical conditions.

**Anoxia and malaria—an experimental study on birds.** H. H. ROSTORFER and R. H. RIGDON (introduced by J. E. Davis). Depts. of Physiology and Pathology, Medical School, Univ. of Arkansas, Little Rock. In previous studies (R. H. Rigdon) it has been suggested that the pathological changes occurring in man, monkeys, and birds with malaria were caused by anoxemia which resulted from the destruction of red blood cells by the malarial parasites. The effect of anoxia on parasitized birds was studied by placing the animals in a decompression chamber at various intervals during the course of the infection. In each of these experiments the parasitized birds died earlier and at a lower simulated altitude than non-malarial controls. The time of death was correlated with the degree of anemia.

In a second series of experiments the course of the parasitemia was followed in ducks kept under anoxic conditions in the decompression chamber. The total number of parasitized cells was greater in these birds compared to the malarial controls kept at atmospheric pressure. However, the percentage of parasitized cells was approximately the same. This variation in the total number of parasitized cells can be accounted for by the polycy-

<sup>1</sup> This work was done under a contract, recommended by the Committee on Medical Research, between the Office of Scientific Research and Development and Columbia University.

themia which results in birds kept under anoxic conditions. These experiments show that death of the malarial birds results from the anemia, and is not related to the total number of parasites per cubic millimeter at any time during the parasitemia.

**The reversal of the cutaneous temperatures of the digits of the upper and lower extremities after extensive sympathectomy.** GRACU M. ROTU and CHARLES SULLARD. *Dept. of Clinical Physiology and Division of Biophysical Research, The Mayo Foundation, Rochester, Minn.* In 1939, Sheard, Roth, Love and Horton reported the case of a patient with complete reversal of the cutaneous temperatures of the digits of the upper and lower extremities after extensive sympathectomy. These results indicated that the regulatory control of the elimination of heat in order that the temperatures of the body may remain practically constant at 98.6° F. had been shifted from the lower to the upper extremities. The question arose as to whether this was the exception or the usual course of events.

Under basal conditions, cutaneous temperatures of the fingers and toes of 117 patients were carried out, before and after sympathectomy, in a constant temperature room maintained at 25.5° C. (78° F.) and a relative humidity of 40 per cent. Bilateral resection of the splanchnic nerves and of the first and second lumbar sympathetic nerves and intervening trunk was performed on 62 patients with essential hypertension. Thirty-five of these patients, or 56.4 per cent, showed a reversal of the cutaneous temperatures of the fingers and toes after operation. Thirty-five patients with occlusive arterial disease of one or both lower extremities had bilateral resections of the first and second sympathetic lumbar trunk in 25 instances and unilateral lumbar sympathectomy in 10 instances. There was no reversal of the cutaneous temperatures of the fingers and toes in this group. When cervicothoracic sympathectomy was performed on 20 patients with Raynaud's disease there was no reversal of the cutaneous temperatures of the fingers and toes. However, in 6 instances the cutaneous temperature of the toes was lower than before the cervico-thoracic sympathectomy.

**Studies on diffusion respiration: II. Recovery following prolonged respiratory arrest.** LAURENCE W. ROTH (by invitation), RICHARD W. WHITEHEAD and WILLIAM B. DRAPER (by invitation). *Dept. of Physiology and Pharmacology, Univ. of Colorado School of Medicine, Denver.* It has been shown (Draper and Whitehead, *Anesthesiol.* 5: 262, 1944) that uptake of oxygen from the atmosphere continues essentially undiminished after respiratory arrest provided, at the time of arrest, the nitrogen in the respiratory tract and atmosphere has been

largely replaced by oxygen. This phenomenon has been termed diffusion respiration.

A series of 12 unoperated dogs was placed in a chamber containing a virtually still atmosphere of oxygen and, after 15 minutes of preliminary denitrogenation, respiration was paralyzed by an overdose of pentothal sodium. Complete respiratory arrest was then maintained for 45 minutes by continued injection of anesthetic. Under these conditions oxygen sufficient for metabolic needs continues to diffuse inwards as the alveolar tension is diminished through the oxygen uptake of circulating reduced hemoglobin. Oxygen saturation of the blood, judged by tongue color, was above normal throughout the period of arrest. Two dogs died after 43 and 35 minutes, respectively, of respiratory arrest. Alveolar gas samples obtained immediately after completion of 45 minutes of respiratory arrest showed CO<sub>2</sub> tensions ranging from 221 to 308 mm. Hg and oxygen tensions ranging up to 192 mm. Hg. The accumulated toxic level of alveolar CO<sub>2</sub> was then eliminated by vigorous artificial respiration. Spontaneous respiration returned in from 3 to 24 minutes. Of the 10 surviving dogs, two died within 24 hours following the experiment. The remainder recovered completely.

Prolonged respiratory arrest due to pentothal sodium overdose, therefore, is not necessarily fatal provided the conditions permit diffusion respiration.

**The fate of carbon monoxide in the body.**<sup>1</sup> F. J. W. ROUGHTON (by invitation) and W. S. Root *Dept. of Physiology, College of Physicians and Surgeons, Columbia Univ.* It has been generally believed that CO is not metabolized or otherwise destroyed in the mammalian body. If so, then all the CO lost from the blood during recovery from poisoning should appear in the expired air. In this case  $B(C_1 - C_2)$  must equal  $V(E_{CO} - I_{CO})$  where  $B$  is the blood volume,  $C_1$  and  $C_2$  are the blood CO contents at times  $t_1$ ,  $t_2$  respectively;  $V$  is the volume of air expired during  $t_1 - t_2$ ,  $E_{CO}$  and  $I_{CO}$  are the respective CO percentages in the expired air and inspired air. In testing this equation on normal men, enough CO was inhaled to saturate the blood about 10 per cent and the expired air subsequently collected for 30 minutes, the  $C_1$  and  $C_2$  samples being drawn at the beginning and end of this period. Of the CO lost from the blood only  $65 \pm 5$  per cent was recovered in the expired air. Theoretical calculation of the maximum rate of CO evolution via the lungs, assuming equilibrium between the alveolar air and blood as regards CO, also gives a figure of 67 per cent recovery in the resting man. The CO lost through the skin, urine and feces can hardly be appreciable; the missing CO may per-

<sup>1</sup> This work was done under a contract, recommended by the Committee on Medical Research, between the Office of Scientific Research and Development and Columbia University.

haps combine with hemoglobin-like pigments distant from the main blood stream, but is more probably lost in reaetions such as hydration to formate and/or oxidation. Further experiments with radio-active tagged CO are planned to test these various possibilities.

**Determination of circulation time with thiamine.** ARTHUR RUSKIN and GEORGE DECHERD (introduced by C. I. Leake). *Dept. of Internal Medicine, Univ. of Texas Medical Branch, Galveston.* Thiamine hydrochloride has a characteristic "nut-like" odor and taste, which may be detected by patients receiving it intravenously. This has been utilized as the basis for measurement of arm-to-tongue (or-nose) circulation time—a method subjective in character, but safe, reproducible, and comparable to previously accepted methods.

In patients without cardio-vascular disease the arm-to-tongue circulation time after injection of 50 to 200 mgs. in the ante-cubital vein was found to vary from 7 to 12 secs., with a single exception (16 secs.). In seven normal children it is 5 to 7 secs. In patients with organic heart disease without congestive failure it varies from 8 to 18 secs.; when congestive failure is evident it may vary from 13 to 30 secs. Rapid circulation was seen in four patients with thyrotoxicosis (6 to 7 secs.), and in two patients with severe anemia (5 to 7 secs.). Uncomplicated essential hypertension and edema not of cardiac origin gave normal results.

These determinations agree closely with the values obtained in the same patients with magnesium sulphate. Amounts up to 300 mgs. of thiamine were required in some patients with congestive heart failure in order to get the effect. Eight per cent of patients tested gave no response to thiamine. A few of these reacted to larger dosage. Suboptimal doses of thiamine may give false high readings, which can be corrected by larger doses. No untoward effects were noted.

**Palmar skin resistance (P.S.R.) as a measurement of occupational fatigue.** A. H. RYAN, L. B. NICE and LOUIS S. CUOLDEN (by invitation). *Dept. of Physiology and Pharmacology, Chicago Medical School.* The method previously described (Ryan and Ranseen, Am. J. Physiol. 142: 68, 1944) consisted of measuring P.S.R. under a standard work stress (one minute on a bicycle ergometer). The present report is on the effect of the length of the working day.

The occupational group consisted of 70 medical students. Thirty-five had additional employment at night averaging  $3\frac{1}{2}$  hours. Average P.S.R. for those not working at night was 1766 ohms and for those who worked, 2017, with standard deviations of 253 and 374 respectively. The difference is highly significant statistically, with a Fisher *t* of 3.26. The highest record was 2800 ohms. For each group the average age was 22 years and sleep habit 7 hours.

There was no significant difference in blood pressure, pulse, body weight and height.

One student who had been working about  $3\frac{1}{2}$  hours nightly changed employment requiring work from 9 PM to 4 AM nightly, necessitating reduced and divided sleep. Immediately before the change, his P.S.R. was 2233 ohms. His P.S.R. rose above 7200 on the twelfth day under the new schedule. On the sixteenth day, he felt exhausted and took a day off for recuperation. A similar event with P.S.R. at 6800 occurred on the twenty ninth day. The average P.S.R. for the month of observation was 4656.

These and previous results suggest that this method may prove useful in establishing, and in determining for individual cases, a critical fatigue level beyond which occupational efficiency may become impaired.

**Post-tetanic potentiation in normal and poisoned unfatigued muscles.**<sup>1</sup> ALEXANDER SANDOW and A. G. KARCZMAR (introduced by Harry A. Charipper). *Washington Square College of Arts and Science.* Post-tetanic potentiation (PTP) of the isometric twitch tension (T) has been observed in directly stimulated unfatigued frog sartorii. The % PTP (the immediate post-tetanic increase of T in % of the pre-tetanic T) in normal muscles may be as high as 50% (for a 5 sec. tetanus). The immediate potentiation gradually disappears roughly exponentially during the ensuing 30-60 min. rest period. The general relation between the PTP and the length of tetanus is unclear, but very short (0.2 sec.) and very long (20 sec.) tetani yield little or no potentiation.

The effect of a poison has been determined by comparing the PTP of any given muscle first in the normal condition and then treated, and allowing for complete recovery from the normal run before immersion of the muscle in the poison. Soaking in 1-1000 M KCN Ringer's for one hour results in an average 30% reduction in the pre-tetanic T, but a 30% increase in the % PTP, and the PTP disappears more rapidly than in the normal controls. 1-40,000 iodoacetate for 1 hr. causes a 15% reduction in T, but no significant change in % PTP.

The tension variations may be correlated with certain changes in the hydrolysis of adenosine-triphosphate caused by the modifications in the muscle's internal chemical milieu resulting from tetanus and the action of the poisons.

**Post-rest potentiation of skeletal muscular contraction.** ALEXANDER SANDOW and MINDA TURKEL (introduced by Harry A. Charipper). *Washington Square College of Arts and Science.* Post-rest potentiation (PRP) is a special type of enhancement of the mechanical response of muscle that we

<sup>1</sup> Aided by a grant from the Penrose Fund of the American Philosophical Society.

have observed immediately following a rest of the order of 5-300 sec. interposed, during the development of fatigue, in an activity series of maximal isotonic twitches at the rate of 1/sec. of directly stimulated frog gastrocnemii. The general PRP sequence begins with an immediate, primary, twitch-height increase relative to the pre-rest twitch, which in 5 to 6 successive contractions decreases rapidly; there follows in the next 7 to 9 twitches a secondary increase in the twitch-height which is then reversed so that the ensuing set of gradually declining contractions approximates to that obtained in the usual fatigue series unbroken by interposed rests. As fatigue develops, the relative primary PRP increases continuously, being most pronounced at total fatigue, but the relative secondary PRP first increases to a point where fatigue is about 50%, and then decreases until it is completely absent in the totally fatigued muscle.

Secondary PRP never appears in muscles from starved animals, and, presumably because of seasonal variations, it may not appear in some well nourished muscles. PRP is not affected by KCN, but both its potentiations show a relative decrease in IAA muscles.

The mechanical behavior in PRP is quite different from that obtained in a twitch activity series after a very long (several hours) rest; the underlying mechanism of PRP must therefore differ from that involved in normal recovery.

Structural alterations in the brain of the albino rat after concussion. H. M. SCHAMP (by invitation) and W. F. WINDLE. *Inst. of Neurology, Northwestern Univ. Medical School, Chicago.* Concussion was produced in 2 albino rats anesthetized lightly with nembutal by striking the movable head with an eccentric pendulum. Six days later they and an anesthetized control animal were killed and perfused with formalin. The brains were prepared for histological study.

No histopathological changes were found in primary motor neurons of the brain stem or spinal cord. Many of the large, medium sized and small nerve cells of the reticular formation of the medulla oblongata, tegmentum of the pons and midbrain as well as many large cells of such nuclei as Deiter's showed marked chromatolysis. The control showed no chromatolysis. This reaction was identical with that previously described in the guinea pig and monkey brain. It differed distinctly from the type of chromatolysis observed after asphyxiation and from that observed after axon section. In the present controlled experiment no peripheral vacuolization of nerve cells such as was reported recently by Tedeschi (*Proc. Soc. Exper. Biol. & Med.*, 57: 266, 1944) after head trauma in albino rats, was observed. The latter type of neuron damage is suggestive of severe asphyxia or of postmortem changes. Uncomplicated concussion is charac-

terized by immediate disorganization of Nissl-body patterns followed by rapidly developing chromatolysis which may culminate in death or recovery of the cells. [Work done under contract, sponsored by CMR, between OSRD and Northwestern Univ.]

Changes in renal clearances following complete ischemia of the kidney. EWALD E. SELKURT (introduced by Carl J. Wiggers). *Dept. of Physiology, School of Medicine, Western Reserve Univ., Cleveland, O.* Renal clearance of creatinine, taken as a measure of glomerular filtration in the dog, and clearance of p-aminohippurate, a measure of effective renal plasma flow, are reduced following the clamping of the renal artery, the reduction being proportional to the duration of ischemia. A 3-5 minute interruption caused an average reduction of 24 per cent. Ten minutes of complete ischemia caused a 72 per cent reduction in clearances, and an almost complete cessation of clearance followed a 20 minute period of clamping. Observations were continued for 136 minutes after the release of the clamp. Control clearances of the right kidney showed no significant changes, nor did mean blood pressure vary significantly.

Two explanations of the reduced clearances are offered: (a) the period of brief ischemia has induced a prolonged vasoconstriction of the renal arterioles; (b) damage to the tubules has resulted from the anoxemia.

These conclusions are based on the following observations: (a) the clearances are influenced to a greater degree than the renal blood flow measured by a direct method; (b) the extraction ratio of hippurate is reduced in proportion to the degree of ischemia; and (c) changes in the concentrating ability of the tubule cells resulted from the ischemia. Such results suggest caution in the use of clearance tests in estimation of renal blood flow under conditions in which renal anoxia exists, as in shock.

Influence of ultraviolet irradiation on anaphylaxis in the guinea pig. W. A. SELLE. *Dept. of Physiology, Univ. of Texas, Medical School, Galveston.* Symptomatic therapy of allergic diseases consists mainly in counteracting effects which might be concerned with the pharmacologic effect of released histamine. It was previously shown that the response of normal intestinal strips to histamine, and of sensitized intestinal strips to shocking doses of antigen, is reduced after ultraviolet irradiation *in vitro*. Attempts were accordingly made to reduce the anaphylactic reaction of guinea pigs by irradiation of the whole animal.

Guinea pigs sensitized to egg white were subjected to increasing daily exposures of ultraviolet light, generated by a Burdick quartz mercury lamp (2900-3200 Å., distance 90 cm.). The hair of the back and neck was removed by barium sulphide. The initial exposure of 2 minutes was increased

90 seconds on each succeeding day. On the 15th day of treatment, the 20th day after sensitization, the 12 animals irradiated and an equal number of untreated sensitized animals were given a minimal shocking dose of antigen by cardiac puncture. Nine control and 10 treated animals died in typical anaphylactic shock. There was thus no evidence that the severity of the anaphylactic reaction is reduced by ultraviolet irradiation.

**Effect of clothing upon the ability of acclimatized men to work at the upper limits of environmental heat.** W. B. SHELLEY<sup>1</sup> (by invitation), L. W. EICHNA<sup>2</sup> (by invitation) and S. M. HORVATH.<sup>3</sup> *Armored Medical Research Lab., Fort Knox, Ky.* A previous study indicated the upper environmental limits of temperature and humidity tolerated by nude men working in hot environments. This study showed that the wet bulb temperature of the environments, rather than the dry bulb temperature or the relative humidity *per se*, was the factor which largely determined the ability of men to work in the heat. The present investigation was designed to determine the effect of clothing upon these limits.

Twelve (12) young men were acclimatized to hot environments which have been shown to be the upper environmental limits tolerated by nude working men. These men performed a daily work load of 4 hours of continuous marching at 3 mph carrying a 20 lb. pack (total energy expenditure, 250 to 300 Cal/hr.). Their performance and physiologic response when clothed in a two-piece coverall of herringbone twill were compared with their reactions when nude. The data taken consisted of hourly heart rates and rectal temperatures, sweat loss throughout the work period and skin temperatures at the beginning and end of work.

Clothing imposes a load which may be expressed in terms of the external environmental load. Wearing one layer of herringbone twill has approximately the same effect as raising the wet bulb temperature of the environment 2°F. to 4°F. This means that nude men can work in environments in which the wet bulb temperature is 2°F. to 4°F. higher than the wet bulb temperature in environments tolerated by clothed working men; e.g., at a dry bulb of 120°F., the nude man can work at a wet bulb of 92°F. whereas the clothed man cannot work if the wet bulb exceeds 88°F.-90°F. This pertains to the average man, individuals are at times capable of better performance.

In addition to lowering the upper limit at which men can work, clothing imposes an added physiologic "cost" on men working in hot environments. For example, at one upper limit at which clothed

men could work for 4 hours (120°F.-88°F.), the following physiologic data were obtained. The data are the average for 12 men.

	Final rectal temperature °F.	Final heart rate/min.	Final skin temperature °F.	Avg. sweat loss gms/hr.
Nude.....	99.7	115	97.0	1125
Clothed.....	100.7	135	97.9	1419

**Influence of ultraviolet irradiation on histamine sensitivity and the Schultz-Dale (anaphylactic) reaction.** VIRGINIA SHEPPERD (by invitation) and W. A. SELLE. *Dept. of Physiology, Medical School, Univ. of Texas, Galveston.* The histamine response of the isolated ileum of the guinea pig, immersed in 1½ cm. of oxygenated Tyrode's solution at room temperature, is reduced approximately 50% after 10 minutes of irradiation with an air cooled quartz mercury lamp (2900-3200 Å., distance 90 cm.). After 20 minutes of irradiation the response (to 10 gamma of histamine base) is only 20% normal; after 40 minutes histamine has little or no effect. If the intestinal segments are kept in the host's serum or plasma during irradiation, the loss of sensitivity is equally rapid.

The anaphylactic response of perfused strips of ileum, taken from a guinea pig previously sensitized to egg white (Schultz-Dale reaction), is also reduced by ultraviolet irradiation. Sensitized strips kept in oxygenated Tyrode's solution and irradiated for 10 minutes display approximately 40% of the normal responsiveness; after 20 minutes of irradiation they are 25% responsive, and after 40 minutes, approximately 10% responsive. Similar intestinal segments irradiated while in the host's serum or plasma, lose their sensitivity to the assaulting dose of foreign protein as rapidly as do segments irradiated in Tyrode's solution.

**Observations on the role of the autonomic nervous system in the diabetic response to alloxan.** ELVA S. SHIPLEY (by invitation), ADELLE RANNEFELD (by invitation) and KARL H. BEYER. *Dept. of Pharmacology, Medical-Research Division, Sharp & Dohme, Inc., Glenolden, Penna.* Experiments have been performed to determine the significance of the autonomic innervation of the pancreas, adrenals, and other upper abdominal viscera in the glycemic changes following alloxan administration in dogs. The procedure consisted of a two stage supradiaphragmatic operation for bilateral vagotomy and bilateral lower thoracic sympathectomy. At least the last six thoracic ganglia and their adjoining chain were removed. Several days later, following repair of the second stage of the operation, the dogs were fasted overnight and then injected intravenously with alloxan equivalent to 75 mgm./kgm. of body weight. Blood

<sup>1</sup> 1st Lt., M.C., AUS.

<sup>2</sup> Major, M.C., AUS.

<sup>3</sup> Captain, SnC., AUS.

sugar values were determined before and after the administration of alloxan.

In unoperated, similarly treated dogs the hypoglycemic phase of the response to alloxan usually reached its lowest level at 8 hours after the injection, and the blood glucose had again reached normal or hyperglycemic levels at 24 hours after alloxan treatment. In the vagotomized, sympathectomized dogs the maximal hypoglycemic response was delayed for 12 to 16 hours and was observed at 24 hours after the injection. A similar delay was observed in the appearance of the hyperglycemic phase of the response to alloxan.

Experiments are in progress to determine the effects of alloxan injections into rats with bilaterally sectioned vagi and with intact adrenals, adrenal enucleation, or complete adrenalectomy. Comparisons are to be made with similarly injected normal adrenal enucleated, and completely adrenalectomized rats with intact vagi.

**Inulin, diodrast and urea clearance studies on aged human subjects.** NATHAN W. SHOCK. *Division of Physiology, National Inst. of Health, Bethesda, Md. and Baltimore City Hospitals, Baltimore, Md.* Fifteen colored males, aged 70-85 years, free from clinical signs or previous history of cardiovascular or renal disease were used as subjects. Inulin, diodrast and urea clearances were determined simultaneously in each subject under basal conditions. Urines were obtained by catheterization and four clearance periods of 15-20 minutes were observed in each subject. Blood levels of 1.5-2.0 mg. per cent diodrast and 15-20 mg. per cent inulin were maintained by continuous intravenous infusion. Urine flows were maintained at 8-15 cc. per minute by oral administration of water. After the four clearance periods, the diodrast blood level was increased to 15-20 minutes were used for the determination of diodrast  $T_m$ .

Average values on a group of 10 colored subjects, aged 30-45 years selected on the same basis did not vary significantly from average results published in the literature. In the aged subjects, the average standard inulin clearance was reduced by 45 per cent. Diodrast clearance was reduced by 60 per cent, so that the average filtration fraction was increased by 35 per cent. The average value for standard  $T_m$  was reduced only 40 per cent so that the insulin clearance per unit of  $T_m$  was within normal limits. Diodrast clearance per unit of  $T_m$  was significantly reduced.

**Effect of subtotal nephrectomy on high-altitude polyuria in the rat.** HERBERT SILVETTE. *Dept of Pharmacology, Univ. of Virginia, Charlottesville.* Six groups of white rats were placed in metabolism cages for 3 hours daily for 30 days under the following conditions: Group I, unoperated controls at room pressure (760 mm. Hg); group II, unoperated controls exposed to a pressure of 282 mm. Hg in

decompression chambers; group III, unilaterally nephrectomized, 760 mm. Hg; group IV, unilaterally nephrectomized, 282 mm. Hg; group V, subtotally nephrectomized (one and two-thirds kidneys removed in a two-stage operation), 760 mm. Hg; group VI, subtotally nephrectomized, 282 mm. Hg.

The urine output of unoperated and unilaterally nephrectomized animals at 760 mm. Hg (groups I and III) average below 0.5 cc. per 100 grams body weight per 3-hour metabolism period. The comparable urine output of unoperated and unilaterally nephrectomized rats exposed to 282 mm. Hg (groups II and IV) averaged between 1.5 and 2.0 cc., there being no significant difference between the two groups. Histological examination of the remaining kidney of groups III and IV rats at the end of the experiment showed slight compensatory hypertrophy, no more marked in the animals exposed to low pressures than in the control animals at room pressure.

Subtotal nephrectomy was followed at 760 mm. Hg (group V) by an increase in urine output equal to that of unoperated animals at a pressure of 282 mm. Hg; but when subtotally nephrectomized animals were exposed to 282 mm. Hg (group VI), their polyuric response was apparently maximal, the urine output averaging between 2.5 and 3.0 cc. per 100 grams per 3-hour period. The histological picture was also significant: tubular hypertrophy and distension were marked, but there was no appreciable injury to the glomeruli. These experiments offer further proof that the polyuria observed at low barometric pressures is a result of failure of tubular (reabsorptive) function. [This investigation has been made with the assistance of a grant from the Ella Sachs Plotz Foundation.]

**Electrocardiographic changes in different nutritional states.** ERNST SIMONSON, AUSTIN HENSCHEL, HENRY LONGSTREET TAYLOR and ANCEL KEYS. *Laby. of Physiological Hygiene, Univ. of Minnesota, Minneapolis.* Definite thiaminosis was produced in 10 men within 16 to 24 days by diets adequate in all respects save thiamine which was substantially zero. The diet and activity of these men were precisely controlled for 5 months prior to this acute experiment. Analysis of average values of repeated electrocardiograms showed:

$$1) K \left( \frac{Q-T}{\sqrt{R-R}} \right) \text{ increased from } 0.384 \text{ to } 0.403, 2)$$

K for mechanical systole (from stethocardiography) increased from 0.319 to 0.332, 3) QRS amplitude ( $\Sigma$  of leads 1, 2, 3) decreased from 27.87 to 23.95, 4) heart rate decreased in nine men from 61.5 to 54.8; one man showed an increase. All these changes were statistically significant. Occasional other changes were not so significant; these included decreases or inversions of T, especially in

leads 2 and 3. Three weeks of thiamine supplementation (5 mg. daily) removed almost all symptoms but there was no recovery of K for mechanical systole or heart rate and only partial recovery of QT interval and QRS amplitude.

Acute starvation with moderately heavy work for  $3\frac{1}{2}$  days of 4 normal subjects produced no change in the ECG in the supine position but the response to tilting to  $65^\circ$  was consistently changed: greater tachycardia, increased right axis deviation, more pronounced decrease of the T Wave in leads 2 and 3. All subjects also showed alterations in QRS amplitude and QT interval but the changes were not uniform. [This work was supported in part under the terms of a contract between the Regents of the University of Minnesota and the Office of Scientific Research and Development. Support from other sources will be acknowledged in final publication.]

**A simple method for the study of biliary tract function in unanesthetized dogs.** W. J. SNAPE<sup>2</sup> (by invitation) and J. E. THOMAS. *Dept. of Physiology of the Jefferson Medical College, Philadelphia.* Unanesthetized dogs with permanently cannulated duodenal and gastric fistulae were used. The duodenal fistula was placed opposite the biliary papilla.

Small, bent, glass catheters of varying diameters with a bulbous enlargement midway between the tip and the elbow were inserted into the common bile duct via the duodenal fistula. A definite point of resistance was encountered as the bulbous enlargement passed the sphincter. The action of the sphincter muscle maintained the catheter in place. The catheter was inserted to an average depth of 18 mm. Incompetence of the sphincter with the catheter in place was proven by failure of the emptied gall bladder to fill.

This method allowed the following observation to be made:

1. Abolishing the effect of the sphincter alone did not result in emptying of the gall bladder.
2. Fresh cream, soured cream, and peptone were effective in emptying the gall bladder, with or without the catheter in place.
3. Sodium sulfate and magnesium sulfate in 5, 10, and 15 per cent solutions when placed in the small intestine failed to cause emptying of the gall bladder either with the sphincter competent or made incompetent by catheter.

**Humoral control of Brunner's glands.** RALPH R. SONNENSCHEIN (by invitation) and A. C. IVY. *Dept. of Physiology, Northwestern Univ. Medical School, Chicago, Ill.* A humoral mechanism for regulation of Brunner's glands was demonstrated by Florey and Harding, who claimed secretin to be the hormonal agent (*Proc. Roy. Soc. B* 117:

1935; *Quart. J. Exp. Physiol.*, 25, 1935). We have used a similar operative procedure, transplantation of the first inch of the duodenum, in four dogs. The observation has been confirmed, in 17 of 22 experiments, that a meal causes an increase in the rate of secretion; this establishes the existence of a humoral mechanism. Ergotamine (0.5 to 1.0 mg.) inhibits this response to a meal (4 experiments).

Crystalline secretin was administered intravenously in twelve experiments, in doses of from 0.1 to 100.0 mg. In nine no change was observed, and in three a questionable increase in the rate of secretion occurred (doses of 0.1 and 4.0 mg.). Injection of a crude, vasodilatant-free secretin preparation; SI, (Greengard and Ivy, *Am. J. Physiol.*, 124, 427, 1938), however, in doses of 8.0 to 15.0 mg., evoked a response in each of thirteen experiments. Ten to 25.00 mg. of the aniline precipitate of SI (secretin-free) caused a definite increase in secretion in four of five experiments. These observations suggest that the results of Florey and Harding may have been due to their use of an impure secretin. Work is in progress to isolate the active factor.

**The effect of electrical stimulation upon strength loss in denervated rat muscle.** SALVADOR ARANA SOTO (by invitation) A. J. KOSMAN (by invitation) S. L. OSBORNE and A. C. IVY. *Dept. of Physiology, Northwestern Univ. Medical School, Chicago, Ill.* The sciatic nerve was sectioned bilaterally in 64 male albino rats and the loss of tension in both gastrocnemii was determined at various stages of atrophy. The greatest strength loss occurs in the first 15 days following denervation (72.3 per cent). At the end of 30 days the denervated muscle retained only 14.8 per cent of its original tension.

No. of animals	Days after denervation	% tension loss
4	5	35.4
5	10	58.5
23	15	72.3
7	18	75.4
5	20	77.8
5	25	81.0
15	30	85.2

In another group of rats the denervated gastrocnemius on one side was stimulated once daily for 15 minutes with a surging 25 cycle alternating current producing 40 contractions a minute. The opposite denervated muscle served as the untreated control.

No. of animals	Days after denervation	% difference tension	% difference weight
20	15	53.6	17.0
16	30	65.2	54.8

<sup>2</sup> Ross V. Patterson Fellow in Physiology and Gastroenterology.

Electrical stimulation of the denervated rat gastrocnemius with a 25 cycle alternating current retards the weight and strength loss of the muscle. [Supported by a grant from the National Foundation for Infantile Paralysis, Inc.]

**Effect of local temperature upon blood flow in extremities.** Lt. C. R. SPEALMAN, II(S), USNR. Naval Medical Research Inst., National Naval Medical Center, Bethesda, Md. Observations of blood volume flow through the hand were made on healthy young men, using the venous occlusion technique. Surface temperatures of the trunk, hands and feet were also recorded. Observations were continued for three hours since approximately two hours are required to establish equilibrium conditions. Results obtained are summarized below, where T(water) indicates the temperature of the water in the plethysmograph, T(finger) indicates the temperature of the free hand, and blood flow (B.F.) is expressed as cc/100 cc/min. Temperatures are given in °C.

	5	10	15	20	25	30	35
T(water).....	5	10	15	20	25	30	35
T(trunk).....	34.4	34.5	34.7	34.8	34.3	34.0	34.2
T(finger)....	28.9	32.3	33.3	33.8	33.3	32.6	32.0
T(toe).....	27.2	31.0	32.9	32.8	32.9	30.6	32.0
B.F. ....	5.1	2.5	1.2	1.2	2.7	5.9	8.9

Blood volume flow is least when hands are moderately cold (15 to 20° C.). When hands are very cold, blood volume flow approximately equals that in warm hands. These observations were made under environmental conditions (D.B. 24° C., W.B., 16° C., with slight air movement) such that the subjects were comfortable with the light clothing worn. Under conditions in which subjects are cold, blood flow is influenced by local temperature in a qualitatively similar manner; however, blood flow is considerably less at any given hand temperature. Observations have also been made under very warm environmental conditions. [The material in this article should be construed only as the personal opinion of the writer and not as representing the opinion of the Navy Department officially.]

**Fixed persistence in the rat of spinal reflex patterns rendered extremely maladaptive by cross union of sensory nerves (motion picture).** R. W. SPERRY (introduced by K. S. Lashley). Harvard Univ., Cambridge, Mass. Nerves of the left hind foot were transected and crossed contralaterally to the peripheral stumps of the corresponding nerves of the right foot, so that after nerve regeneration the right foot was reinnervated only by nerves that originally had supplied the left foot. This led in all cases to erroneous contralateral localization of stimuli applied to the reinnervated foot and also to a reversal of hind limb reflexes initiated through the crossed sensory nerves.

Although extremely maladaptive, the reversed reflex reactions nevertheless persisted without inhibition or correction by central nervous readjustment. A full printed account of the experiments is reported in J. Comp. Neur., vol. 78, pp. 59-90.

**Anticonvulsant effects of steroids.** E. A. SPIEGEL and H. T. WYCIS (by invitation). Dept. of Experimental Neurology, Temple Univ. Medical School, Philadelphia, Pa. Continuing former studies (E. Spiegel, Feder. Proc. 2, no. 1, 1943) anticonvulsant effects were observed on white female rats with androstenedione, dehydroandrosterone, desoxycorticosterone acetate, acetoxy-pregnolone, progesterone, and testosterone. The following substances had no or only a questionable anticonvulsant action: cholesterol, allocholesterol, cholestryl bromide, epicholestanol, stigmastanol, stigmasteryl acetate,  $\alpha$ -spinasteryl acetate, ergosterol, ergosteryl acetate,  $\alpha$ -ergostenyl acetate, dehydrocholic acid, desoxycholic acid,  $\Delta^5$ -3-acetoxycholenic acid, sarsasapogenin acetate, pseudo sarsasapogenin acetate, diosgenin acetate, pseudo diosgenin acetate,  $\alpha$ -estradiol benzoate (progynon B), theelin in oil, 6 ( $\alpha$ ) acetoxy-progesterone (amorphous modification), etio-cholan-3 $\beta$ -ol-17-one acetate, 5 pregnen-3 $\beta$ -ol-20-one acetate, 5, 16 pregnadien-3 $\beta$ -ol-20-one acetate, stilbesterol. The anticonvulsant dose lies rather close to or is identical with the hypnotic dose for testosterone, progesterone and desoxycorticosterone; a definite margin between these doses exists for adrostenedione, dehydroandrosterone and acetoxypregnenolone. [Aided by a grant from the Schering Corp.]

**Influence of retinal impulses upon vestibulo-ocular reflex arc.** E. A. SPIEGEL and N. P. SCALA (by invitation). Dept. of Exper. Neurology, Temple Univ. Medical School, Philadelphia, Pa. Lesions of the optic tract or of the external geniculate body were produced electrolytically in cats under nembutal anesthesia, the needle being introduced by means of a Horsley-Clarke stereotaxic apparatus; or the optic tract was cut after it had been exposed by the technic of the overhanging brain. A marked difference between the postrotatory nystagmus following clockwise rotation and that following counterclockwise rotation was observed postoperatively. The duration of the postrotatory nystagmus to the operated side reached up to three times, the number of its jerks up to four times the corresponding values of the nystagmus to the normal side. This prevalence of the nystagmus to the operated side could be observed for several months following the operation. These observations seem to indicate that impulses from the homolateral halves of the retinae have an inhibitory effect upon vestibulo-ocular reflexes tending to produce nystagmus to the same side.

The effects of intra-arterial administration of

acetylcholine on gastric secretion and motility. GEORGE W. STAVRAKY. *Dept. of Physiology, Univ. of Western Ontario Medical School, London, Canada.* In over 40 experiments on anaesthetized dogs, acetylcholine chloride and acetylcholine bromide were introduced into various branches of the gastric arteries.

When injected into a quiescent stomach (alkaline reaction of the mucosa) acetylcholine had a tendency to evoke different responses from different regions of the viscera. Gastric juice secreted from the lesser curvature was of low acidity but contained large quantities of mucus and pepsin; for the most part free HCl was absent from it and the total chloride was low (127.2-145.8 m.eq./l.). An abundant flow of alkaline gastric juice was usually obtained from the greater curvature of the stomach, this sometimes following an initial period of acid secretion; the alkaline gastric juice (pH 7.6-8.9) contained variable amounts of dissolved, opalescent mucus but no pepsin, and the total chloride in it varied between 94.5-144.3 m.eq./l. Also, from the pyloric region of the stomach a secretion of alkaline mucus was obtained, the latter however being not opalescent but clear. When introduced into a secreting stomach (histamine), dilute solutions of acetylcholine increased the output of acid and pepsin, whereas more concentrated solutions reduced the acidity and the total chloride of the gastric juice, but markedly increased the output of pepsin and mucus. All these effects of acetylcholine were enhanced by eserine and reduced or precluded by atropine.

Intra-arterial administrations of acetylcholine often greatly increased the motility of the stomach. In several experiments an hour-glass contraction of the stomach developed, completely separating the pyloric region from the body of the stomach so that simultaneously, alkaline mucus was collected from the former and acid gastric juice from the latter.

**Studies on the effects of an antispasmodic compound on the colon activity in dogs.** F. R. STEGGERDA, A. B. TAYLOR (by invitation) and JUSTIN HOEKSTRA (by invitation). *Dept. of Physiology, Univ. of Illinois, Urbana.* The effects of various doses of an antispasmodic compound (Abbott Laboratories) in combination with certain amounts of nembutal were studied in unanesthetized dogs whose colons had previously been made opaque to x-rays with thorotrust.

The activity of the colon was recorded by means of a modified catheter inserted directly into the colon via the rectum. This apparatus was made leak proof by passing the catheter through an improvised rubber funnel cemented to the anus. This preparation provided for the injecting of known quantities of gas into the colon and the recording of pressure changes by means of a water manometer. The permanent visualization of the colon to x-rays

with thorotrust made it possible to make a picture of the exact changes which occurred in the colon.

The results indicate that the colonic tone and contraction waves, resulting from distention with gas, show a progressive tendency to decrease with intravenous injections of 10 to 40 mg of the antispasmodic compound. When small amounts of nembutal (30 mg) were given intravenously at the time of the administration of the compound, the effects were increased by at least 50%. That the effects of the nembutal are not specifically on the colon musculature is shown by its ineffectiveness when similar comparisons are made on isolated strips.

The results suggest that nembutal reflexly affects the colonic musculature and thereby allows its increased susceptibility to the antispasmodic compound.

**Effect of hyperglycemia on the motility of the small intestine of the dog.** J. CLIFFORD STICKNEY, DAVID W. NORTHUP and EDWARD J. VAN LIERE. *Dept. of Physiology, School of Medicine, West Virginia Univ., Morgantown.* Belenkov (Fiziologicheskii Zhurnal SSSR 30, 704, 1941) has reported that intravenous glucose inhibits the motility of the small intestine of dogs with Thiry-Vella loops. Since there has been considerable conflicting evidence in regard to this problem, we have reinvestigated it on dogs with a technique (Macht's) which has been used extensively in studying intestinal motility in this laboratory.

Fifty cc. of a charcoal-acacia mixture was given by stomach tube to 37 unanesthetized dogs; after 3 min. 1.5 g. glucose per kg. as a 25 per cent solution was given intravenously to 19 of the dogs, while 18 were given an equivalent volume of saline intravenously. Twenty-five min. after intubation, blood was drawn for sugar analysis (Folin and Wu method). Thirty min. after intubation the dogs were given a fatal dose of ether, the small intestine was removed and the distance the charcoal mixture had traversed, measured.

The average blood sugar of the control dogs was 99 mg. per 100 cc., while that of the experimental dogs was 285 mg. The average distance traversed by the charcoal mixture in the control dogs was 183 cm. and in the hyperglycemic dogs, 141 cm. The difference, 42 cm. (23 per cent), is statistically significant, and it is concluded that severe hyperglycemia retards the motility of the small intestine of the average dog.

**The emptying of the human stomach as influenced by the nutrient composition of the meal.** ANGIE MAE STURGEON (by invitation), AUSTIN HENSCHEL and ANCEL KEYS. *Laby. of Physiological Hygiene, Univ. of Minnesota, Minneapolis.* The influence of test meal composition on rate of gastric emptying was studied in 8 normal young men who had been for months on a carefully stand-

ardized dietary. The control test meal was a standard cooked oatmeal-barium sulphate mixture. In the experimental test meals, part of the oatmeal was isocalorically replaced with either sugar, butterfat, hydrogenated vegetable shortening or lactalbumin to give high carbohydrate (85% of calories), fat (70% of calories) or protein (55% of calories) meals. The calorie content and weight of all test meals was constant. Roentgenograms of the stomach were taken at 5, 30, 60 and 90 minutes after the test meals were eaten and from then on the progress of the meal was followed by means of fluoroscopy. The final emptying time was confirmed by a roentgenogram. Statistical analyses of the per cent of the original meal emptied by the stomach at the various time intervals and the time required for complete emptying of the stomach revealed no significant difference (1) in rate of emptying or final emptying time between the control test meal and either the high carbohydrate, high fat or high protein test meals, (2) in rate of emptying through 90 minutes between the high carbohydrate, high fat and high protein test meals, (3) in final emptying time between the high fat and either the high carbohydrate or high protein meals. The final emptying time for the high protein meal was, however, significantly longer (average  $\pm$  51 mins.) than for the high carbohydrate meal.

Determination of man's blood pressure on the human centrifuge during positive acceleration.<sup>1</sup> R. E. STURM (by invitation), E. H. Wood and E. H. LAMBERT (by invitation). *Acceleration Lab., Mayo Aero Medical Unit, Rochester, Minn.* An apparatus consisting of the following parts has been devised for the indirect determination of man's systolic blood pressure on the human centrifuge: (1) an inflatable cuff surrounding the wrist; (2) a magnetically operated inflating valve, which on opening raises the cuff pressure 40 mm. of mercury; (3) a constant leak, deflating the cuff approximately 10 mm. of mercury per second; (4) a photo-electric opacity pulse detector on a finger distal to the cuff and (5) an adjustable electronic synchronizer, which opens the magnetic inflating valve in response to impulses received from the photo-electric pulse detector.

In operation, the cuff pressure is raised above systolic blood pressure. The constant leak then slowly reduces this pressure. When a systolic pressure peak pushes a pulse wave past the cuff, it is detected in the finger. The pulse activates the magnetic valve, which instantly raises the cuff pressure 40 mm. of mercury. By simultaneously recording the finger pulsations and the wrist cuff pressure a determination of systolic blood pressure

at the wrist is obtained every three or four heart beats.

During exposure to positive acceleration the blood pressure at the level of the eyes fell approximately 20 to 30 mm. of mercury per g increase in acceleration. The maximal fall occurred within seven seconds and was followed by recovery of the blood pressure level while acceleration was maintained. Thus like other physiologic changes in man during positive acceleration, the blood pressure displays a period of failure followed by a period of compensation.

The effects of explosive decompression and the extent to which it has been proved safe for young healthy subjects. H. M. SWEENEY and M. H. JOFFE (by invitation). *Acro Medical Lab., Wright Field, Dayton, O.* The principal operational hazard in pressurized aircraft has been considered to be the effect of sudden loss of the pressure differential (explosive decompression) on aircrews.

The degree of explosive decompression which one can withstand safely is determined by the extent and/or rate of expansion of the gases in hollow viscera. Of the four pertinent factors involved in explosive decompression, two, the pressure differential and the flight altitude, regulate the extent of expansion, while three, namely the pressure differential, the volume of the pressurized compartment, and the size of the aperture, regulate the rate of expansion. The damaging effect on the lungs from decompression in cases where the expansion is greater than can be accommodated without stretching the tissues beyond physiological limits (which experimentally and theoretically appears to be an expansion greater than 2.3 times the initial volume), depends upon the rate of decompression; if the expansion is less than 2.3 times, the effects are independent of rate.

At the moment of decompression, the subjects experienced a sense of inflation in the chest and abdomen and a rush of air from the mouth and nose. Slight twinges of pain were felt by a few subjects in the upper abdominal region, possibly a result of stretching the attachments of the dia-

*Condensed data of explosive decompression experiments on human beings*

Diameter of Open ing in 45-cu.in. cuff	PSI differen- tial press	Simulated altitude		Time of decom- pression	Rate of decom- pression PSI/ sec.	Expansion of body gases no. of times	Rate of expansion vol./ sec.	Comparable size of hole in 1000-cu.ft. compartment
		Cabin	Flight					
in.	feet	feet	sec.					
12	6.55	10,200	35,000	0.075	87	3.5	47	66
12	7.50	8,000	35,000	0.090	83	3.9	43	66
27	1.50	34,000	45,000	0.008	143	2.3	288	
27	1.25	37,000	45,000	0.006	167	2.3	383	
27	1.00	40,000	50,000	0.005	200	2.3	460	

<sup>1</sup> Work done under contracts with: (1) United States Army Air Forces, Wright Field, Dayton, Ohio, and (2) the Office of Scientific Research and Development, National Research Council, Washington, D. C.

phragm, during the more drastic decompressions. Few cases of gas pain were encountered, and roentgenograms to depict the amount of gas harbored in the gastrointestinal tract did not show any positive correlation. Ear pain was not experienced.

**Physiology of the visual cell.** S. A. TALBOT. *Wilmer Ophthalmological Inst., Johns Hopkins Medical School, Baltimore, Md.* Recent evidence from optics and neurophysiology provides a connection between the fine structure of the photoreceptor and nerve frequency evoked by light.

Optical properties of lamellae, of myeloid structure, and rhodopsin indicate that light is concentrated at and excites only the alternate protein-lipoid interfaces. Photodecomposition is limited by stereochemical factors, supporting Moon and Spence's kinetics. Quarter-wave interference in lipoid layers causes a strong exponential decrease of intensity with cell length. Moreover, the extraordinary refractivity of oriented carotene present, increases the index of protein layers with dark-adaption. These factors, not absorption, explain quantitatively the logarithmic response law (Hecht), and changing ranges of response to flashes (Granit). A separate non-excitatory surface- and volume-photolysis governs levels of random discharge (peripheral threshold).

Electronic depolarization by one photon of excitatory light at the proximal interface of one lipoid layer, just exceeds Brownian fluctuation. This depolarization must be amplified in each lamella, probably by acetylcholine (Hecht's reactant L), to operate physiologically. The resulting drop of resistance connects in series the pile of distal interface potentials, which then actuate the propagative nerve-membrane via an extracellular circuit. This summated differential voltage controls frequency of discharge, as demonstrated by Barron and Matthews in spinal cord.

Principles of Lippmann photography explain the lengths and efficiency of rods and cones, but must be supplemented by separate pigments to account for saturation in color vision. At least three pigments are required, though bipolar connections and cone-structure permit one to be rhodopsin. [The support of the Markle Foundation is gratefully acknowledged.]

**A multiple cassette changer for studying colon activity.** A. B. TAYLOR (by invitation), JUSTIN HOEKSTRA (by invitation) and F. R. STEGGERDA. *Dept. of Physiology, Univ. of Illinois, Urbana.* A multiple cassette changer, equipped to handle fourteen cassettes, has been developed to facilitate the study of the functioning of the dog's colon previously visualized with thorium dioxide. Frequency of contraction, rate of propulsion, and colon size under atmospheric conditions as well as various negative pressures in a decompression chamber have been studied. Dogs were usually

starved for twenty four hours prior to experimentation and were anesthetized with nembutal. Colon areas were measured by means of a planimeter.

In the cassette changer, a series of gears driven by a synchronous motor releases a cassette containing an unexposed film from a lead lined storage box at any one of the following time intervals desired: one per second, one per two seconds, one per five seconds, one per ten seconds, one per fifteen seconds, one per thirty seconds, one per minute, one per two minutes, one per three minutes, one per four minutes, one per five minutes, and one per ten minutes. Each cassette is moved on a motor driven belt to a position under the animal where it is exposed simultaneously with the release of the next cassette. Movement of the second cassette into exposure position pushes the exposed cassette into a second lead lined storage box.

Exposure is controlled by means of a mechanical arm operated by the gear mechanism. This arm closes a switch connected to the x-ray machine simultaneously with the release of the cassette from the first lead lined box. The mechanism allows variation in exposure time from approximately 1/50 of a second to any longer interval desired. This apparatus also offers an opportunity for studying the functioning of various other visualized organs of the body.

**Heat tolerance for short exposures.** CRAIG L. TAYLOR (introduced by A. P. Gagge). *Aero Medical Lab., Wright Field, Dayton, O.* The limits of temperature and humidity which are tolerable for short periods of exposure have been determined for sitting men dressed in light-weight cotton underwear and coveralls. Experiments were conducted in an all-weather room permitting control of dry and wet bulb temperatures within  $\pm 2^{\circ}$  C. Average skin temperature, from thermocouples located at six points on the skin surface, rectal temperature and heart rate were determined before entering the hot room and periodically during exposure. Sweat loss was calculated from the nude body and clothing weights taken before and after exposure.

In the first series four subjects previously acclimatized by four days of work in the heat were given 16 tests at various temperatures and humidities. Heart rate, skin and rectal temperature, and sweat loss data were averaged for each subject to yield an index of physiological response. The following regression formula was then developed:

Index = 0.085 (DB)  $\pm$  0.057 (VP) - 5.82  
where, DB = dry bulb temperature in degrees C.

VP = vapor pressure of the atmosphere in mm. Hg.

Values of index, which were considered to be valid and safe for 30 and 60 minute exposures, were then selected from inspection of the data at hand and from results of further exploratory tests.

Finally, the 30 and 60 minute limits calculated from these indices were verified by testing two groups of unacclimatized subjects at various points on the curves. The tolerance limits for unacclimatized military personnel (and terminal rectal and skin temperatures, and heart rates from these experiments) are shown in the following tabulation:

Limit	Environmental temp. (°C.)			Mean terminal responses		
	Rel. hum. (%)			Rectal temp. ("C.)	Skin temp. ("C.)	Heart rate
	10	50	90			
30 minutes .....	67	50	42	38.1	38.7	128
60 minutes.....	63	47	40	38.2	38.2	123

The circulatory changes in man induced by bed rest and alterations in activity.<sup>1</sup> HENRY LONGSTREET TAYLOR, AUSTIN HENSCHEL, LESTER ERICKSON (by invitation) and ANCEL KEYS. *Laby. of Physiological Hygiene, Univ. of Minnesota, Minneapolis.* Six normal young men were kept in strict bed rest for three weeks. The bed rest was preceded by a month of standardized activity and diet and was followed by 6 to 10 weeks of reconditioning. Bed rest produced important changes in several cardiovascular variables. The resting pulse rate (in bed) increased 10 (a.m.) and 18 (p.m.) beats per minute. The systolic heart volume decreased 91.4 ml. (16.2%). The walking pulse rate (3.5 m/h and 10% grade) increased 40 beats per minute. The postural adjustment score decreased 64.2 Crampton points. The oxygen transport during a 90 second "anaerobic" run (7 m/h and 15% grade) was decreased by 720 ml. (16%) and the blood lactate 15 minutes after this standard work was increased by 19 mgs%. Blood volume (T-1824) was decreased by 572 ml. or 9.3%. Bed rest had no effect on cardiac output, renal blood flow (P-amino hippurate) or the efficiency of either aerobic or anaerobic work. With a standard reconditioning regime, recovery of function was achieved in the following order: lactate after "anaerobic" work (2 weeks), work pulse and oxygen transport in "anaerobic work" (not more than six weeks) and postural adjustment at least two months. Cardiovascular deterioration appears to be one of the principle elements in the debility produced by bed rest.

A further study of the innervation of the pancreas—the action of drugs of the atropine group. J. E. THOMAS and J. O. CRIDER. *Laby. of Physiology of the Jefferson Medical College.* The secretory

response of the pancreas to peptone, soap, or HCl in the intestine or to intravenous secretin was studied in unanesthetized dogs before and after administration of atropine or hyoscymine. The usual dose of atropine (sulphate) was 0.2 mg. and of hyoscymine (hydrochloride) was 0.1 mg. per kilogram.

The specific gravity and total nitrogen (mg./cc.) of the pancreatic juice were decreased by the action of these drugs regardless of the stimulus used to promote secretion. When the stimulus was soap, HCl or secretin the volume of secretion and total nitrogen output were also reduced. The response to soap was decreased most, that to secretin least. When the stimulus was peptone an increase in volume of secretion usually followed administration of either drug. In two animals the increase was pronounced, amounting to several times the normal volume. The effect on total nitrogen output was not constant but an increase was common.

The fact that the parasympathetic depressants decrease the response to secretin is surprising and contrary to results obtained by others in anesthetized animals. Probably "tonic" cholinergic reflexes normally augment the response to secretin in unanesthetized animals. The results with soap and HCl indicate that these agents stimulate the pancreas in part through a nervous mechanism. The experiments provide no basis for conclusions regarding the mechanism through which peptone stimulates the pancreas.

The effects of the thyroid and the adrenal cortex on oxidation enzymes of rat liver. SAMUEL R. TIPTON, ISABEL H. TIPTON (by invitation) and MARTHA JEAN LEATH (by invitation). *Univ. of Alabama School of Medicine, University.* A study of the effects of feeding dessicated thyroid gland, of adrenalectomy, and a combination of the two on the total succinic acid oxidase and the cytochrome oxidase activities (determined on aliquots from the same homogenate) was made on livers of white rats. Feeding 400 mgms. dessicated thyroid daily results in an increased activity of succinic dehydrogenase and cytochrome oxidase; the effect on the dehydrogenase being more marked. Subcutaneous injection of 0.5 mgm. of thyroxine daily resulted in an increase in the enzyme activities also but was less effective than dessicated gland. Administration of 0.5 mgm. of thiamin daily to the thyroid-fed rats resulted in a further increase in the activity of the dehydrogenase and of the cytochrome oxidase. Four to ten days after the adrenalectomy there is a decrease in activity of both enzymes, the cytochrome oxidase being affected more markedly. Feeding thyroid to adrenalectomized rats leads to severe hypoglycemia and is rapidly fatal. However, removal of the adrenals from rats after seven to twelve days of thyroid feeding appeared to prevent further increase in enzymatic activity, and the

<sup>1</sup> This work was supported in part under the terms of a contract between the regents of the University of Minnesota and the Office of Scientific Research and Development. Support from other sources will be acknowledged in final publication.

resulting average dehydrogenase and oxidase activities are not as high as those found in rats fed thyroid for equivalent periods.

**Cortical responses to cortical stimulation in relation to the spontaneous EEG of the rabbit.** J. E. P. TOMAN (introduced by C. Fenning). *Dept. of Pharmacology and Physiology, Univ. of Utah School of Medicine, Salt Lake City.* Insulated epidural electrodes were used for stimulation and recording in seven rabbits. Non-convulsive EEG responses to single thyratron shocks were observed at all levels of excitability from deep surgical anesthesia to convulsive seizures. These "secondary" discharges were relatively independent of shock intensity above threshold, and were reproducible from a given cortical area at a given level of excitability regardless of the area stimulated. Responses varied from 0.5 to 2.0 sec. in duration. In the motor cortex of normal animals awake or drowsing, the responses were characterized by an initial surface-positive spike of 0.2 sec. latency, followed by a complex of waves closely resembling the spontaneous "spindles" from the same animal in sleep or light barbiturate sedation. Test shocks revealed relative refractoriness up to 0.2 sec. Facilitation was occasionally seen at intervals from 0.2 to 0.3 sec. Summation of subnormality occurred with longer intervals and repeated shocks. Slow periodic waxing and waning in size and duration of responses were observed, with cycle lengths from 10 to 20 sec.

After sub-convulsive metrazol doses, the responses resembled the spontaneous "petit mal" bursts from the same area, while in deep barbiturate anesthesia they reverted to single complex waves of long refractoriness, resembling spontaneous activity at the same level.

It is suggested that these responses represent a maximal temporary synchronization of mechanisms capable of contributing to cortical spontaneous activity at any given level of excitability.

**Excitation constants for electroshock seizures in rabbits.** J. E. P. TOMAN (introduced by C. Fenning). *Dept. of Pharmacology and Physiology, Univ. of Utah School of Medicine, Salt Lake City.* Using a standard electroshock apparatus for 60-cycle stimulation, and determining the seizure threshold electroencephalographically, strength-duration curves were obtained for five normal unanesthetized rabbits with permanently implanted epidural electrodes. Mean values are tabulated below. The data were not satisfied by the usual relation,  $k_1 = 2.3(\log(I) - \log(I_0))/t$ . A better approximation was found by  $k_2 = I_0/It(I - I_0)$ . For motor responses occurring only during the period of stimulation, the threshold remained practically constant at the convulsive rheobase over the entire range of durations.

No appreciable accommodation was found to

slowly increasing 60-cycle stimulation with durations up to 80 minutes. With continuous stimulation by current above threshold, alternating seizures and depression with summation of subnormality were seen, but electronarcosis was not observed.

t (sec)	I (rheobases)	$k_1$ (sec) $^{-1}$	$k_2$ (rheobase sec) $^{-1}$
0	1.4	0.14	0.20
5	1.6	0.20	0.21
3	1.9	0.25	0.19
1	2.8	0.44	0.20
0.5	3.8	0.60	0.19
0.2	5.8	0.95	0.18
0.1	7.9	1.35	0.18
0.05	11.8	1.75	0.16

**Observations on fatigue: the release from working muscle of agents depressing acetylcholine synthesis and with apparent curare-like action.** CLARA TORDA and HAROLD G. WOLFF. *New York Hospital and the Depts. of Medicine (Neurology) and Psychiatry, Cornell Univ. Medical College, New York City.* The amount of contraction of the gastrocnemius muscle of frog during stimulation of the sciatic nerve was investigated after intraventricular injection of serum obtained from the limb of cat with occluded circulation after: 1) passive movements; 2) intermittent; and 3) continuous electrical stimulation of the sciatic nerve.

In the presence of serum from passively moved limbs the contraction decreased by 35%. Serum from limbs after intermittent stimulation did not modify the contraction. In the presence of serum from limbs after continuous stimulation the contraction decreased by 20%.

It is therefore likely that during performance of muscle work substances are released into the blood that decrease the muscle contraction induced by indirect stimulation. The effect of these substances was less apparent when the stimulation of the muscle originated through the motor nerve (propagation of excitatory state from the nerve, release of acetylcholine-like substance).

Since it is likely that during performance of prolonged muscle work an acetylcholine-like substance is synthesized locally, the effect of serum obtained after prolonged work on acetylcholine synthesis was also investigated.

In the presence of serum from arms with occluded circulation after repeated fist formation 40% less acetylcholine was synthesized than in the presence of control serum.

Assuming that the biochemical changes responsible for these results occur also with adequate blood supply, muscle fatigue would be partly a result of the decreased acetylcholine synthesis at the motor end plate, and perhaps also of a decreased

response of muscle cell to the acetyl-choline-like substance released.

A study of the work capacity of college women. W. W. TURTLE. *Dept. of Physiology, State Univ. of Iowa, Iowa City.* By use of a bicycle ergometer the work capacity of 146 college women in various fields of activity, was studied. The group included 62 student nurses, 24 who participated in regular physical activity, and 60 picked at random. The procedure was to have each subject ride the bicycle as fast as possible for two minutes. The load employed was 3 amperes of field current which resulted in a work output of 1500 Kgm. at 60 pedal cycles per minute.

The data show that those participating in regular physical activity excel in all phases of work measured. As compared to the unselected group, they performed 20 per cent more work, attained a 16 per cent higher maximum work rate and maintained a 12 per cent higher fatigue level. The data also show that the student nurse group is significantly less capable of doing work than the random sampling group. As compared to the unselected group, they performed 11 per cent less work and maintained a 12 per cent lower fatigue level. They were, however, able to equal the maximum work rate of the unselected group.

It is evident from the data that those who participated in a regular program of physical activity excelled in dynamic physical fitness while those who pursue courses which are crowded both academically and professionally suffer from a lack of systematic physical training.

The effect of iodoacetate and malonate on the respiration of various regions of the brain. DAVID B. TYLER. *California Inst. of Technology, Pasadena.* It is now well known that the resting respiration of the different regions of the brain varies in intensity. Recent work of Gerard (Amer. J. Physiol. 136, 49, 1942) indicates that the magnitude of this respiration depends on the whole protoplasmic mass of the area. He demonstrated that the oxygen uptake of tissue bits from various regions of the frog's brain was the same when related to the total protoplasmic mass. We have found that the respiration of the various regions of the brain is affected differently by two inhibitors. By means of Warburg respirometers, it was noticed that iodoacetate ( $10^{-4}$ M) depressed the respiration of medullary tissue the most, while the pallium and stem were  $\frac{2}{3}$  to  $\frac{1}{2}$  as sensitive. With malonate ( $10^{-2}$ M), the reverse effect was observed. With this inhibitor the pallium was most sensitive, while the respiration of the medulla was least affected. Studies that are under way at this time are designed to determine whether this phenomena is related to the proportion of white matter present in the various regions, or whether they are due to

cellular metabolic differences of the various regions.

The effect of anoxic anoxia on water distribution in the body. EDWARD J. VAN LIERE and JOHN JOSEPH LAWLESS (by invitation). *Dept. of Physiology and Anatomy, School of Medicine, West Virginia Univ., Morgantown.* Three groups of albino rats under carefully controlled conditions were subjected in a low pressure chamber for 3½ hours to the following barometric pressures: Group A, 564 mm. Hg; group B, 379 mm. Hg; group C, 246 mm. Hg, corresponding, approximately, to altitudes of 8,000, 18,000 and 28,000 feet, respectively. Simultaneously, control groups were kept in containers which were placed along side of the low pressure chamber.

The water content of the following organs were determined: cerebrum, kidney, liver, muscle, skin and adrenal glands. The water content was determined by drying the tissues in an oven at 105° F. until two successive weighings varied by 0.5 mgm. or less.

At each elevation all of the animals lost a significant amount of weight as compared to the control animals.

With reference to the tissues studies the following results were obtained: At a barometric pressure of 564 mm. Hg no appreciable change in water content was observed in any of the tissues; at 379 mm. Hg both muscle and skin tissue showed a significant decrease in water content; at 246 mm. Hg the skin still showed a significant decrease in water content, but the muscles did not. The adrenal glands, however, showed a significant increase in water content at 246 mm. Hg pressure.

Treatment of experimental renal hypertension with hog renal extract fractions. G. E. WAKERLIN, OLIVER KANN (by invitation) and WAYNE DONALDSON (by invitation). *Dept. of Physiology, Univ. of Illinois College of Medicine, Chicago, and Research Labys., Parke, Davis & Company, Detroit, Mich.* In order to throw further light on the mechanism of the anti-hypertensive potency of hog renal extracts previously reported (Am. Ht. J., 25: 1, 1943 and J. Pharm. & Exper. Ther., 81: 101, 1944) and to effect a possible concentration and purification of the active principle, we gave daily intramuscular injections of four hydroalcoholic fractions of partially purified hog renal extract containing renin in a dose of 5 Gm. equivalent of fresh renal cortex per Kg. for six months. None of the eight hypertensive dogs treated (two for each fraction) showed any significant change in blood pressure. The dogs receiving the two fractions retaining the larger amounts of original renin activity (100 and 20 per cent respectively) showed antirenin in their serums whereas the other dogs did not. Each of the four fractions produced significant local inflammatory effects.

Somewhat similar results were obtained with three hydroacetone fractions.

We subjected partially purified hog renal extract containing renin to dialysis, the concentrated dialysate containing none of the renin activity and the dialysis residue retaining 25 per cent. The hypertensive dogs treated with the dialysate in a 10 Gm. equivalent dose for six months showed no significant change in blood pressure and no antirenin. The two dogs similarly treated with the dialysis residue, on the other hand, showed a reduction to the normotensive level in one case and to a near normotensive level in the other, with antirenin demonstrable in their serums.

We are now studying the possible antihypertensive potency of four other hog renal extract fractions. [This work was aided by grants from the John and Mary R. Markle Foundation, Parke, Davis and Company and the Graduate School Research Fund of the University of Illinois.]

**Relation of amount of renal tissue to antihypertensive effect of renal extracts in experimental renal hypertension.** G. E. WAKERLIN, OLIVER KAMM (by invitation) and WAYNE DONALDSON (by invitation). *Dept. of Physiology, Univ. of Illinois College of Medicine, Chicago, and Research Labys., Parke, Davis & Company, Detroit, Mich.* Recent observations suggest that renal hypertensive dogs with two renal artery constricted kidneys are more difficult to influence therapeutically with renal extracts than hypertensive dogs subjected to unilateral renal artery constriction and subsequent nephrectomy. Thus two dogs showing a good to excellent therapeutic effect with highly purified hog renin intramuscularly in a 3 Gm. equivalent dose of crude renal cortex (30 Goldblatt units of renin) per Kg. daily for six months, were one kidney animals, whereas three animals showing only a fair decrease in blood pressure with the same dose of highly purified hog renin were two kidney dogs. Likewise six dogs treated with partially purified hog renal extract containing renin and showing an excellent response were, with one possible exception, one kidney animals, whereas two dogs treated with partially purified hog renal extract containing renin, and showing only fair responses, were two kidney hypertensive dogs. These findings further suggest that the pathogenesis and mechanism of experimental renal hypertension involve some type of pressor or hypertensive effect by kidneys with constricted renal arteries rather than a decrease in normal renal antipressor or antihypertensive activity recently suggested by Grossman and his co-workers. [This work was aided by grants from the John and Mary R. Markle Foundation, Parke, Davis & Company and the Graduate School Research Fund of the University of Illinois.]

Treatment of experimental renal hypertension

with hog renal extracts. G. E. WAKERLIN, OLIVER KAMM (by invitation) and WAYNE DONALDSON (by invitation). *Dept. of Physiology, Univ. of Illinois College of Medicine, Chicago, and Research Labys., Parke, Davis & Company, Detroit, Mich.* In a further study of the mechanism of the antihypertensive potency of hog renal extracts previously reported (Am. Ht. J., 25:1, 1943 and J. Pharm. & Exper. Ther., 81:101, 1944) we treated two hypertensive dogs each for six months daily and intramuscularly with partially purified hog renal extract containing renin in a 2 Gm. equivalent dose of fresh renal cortex (20 Goldblatt units of renin) per Kg., with heat-treated partially purified hog renin in a 2 Gm. dose, and with hog renal medulla extract prepared after the manner of partially purified renin in a 2 Gm. dose. The partially purified hog renal extract containing renin showed usual (100 per cent) renin activity, the heat-treated hog renin, 5 per cent; and the renal medulla extract (because of admixture with renal cortex), 20 per cent. To our surprise the 2 Gm. dose of partially purified hog renal extract containing renin produced only slight reductions in blood pressure, antirenin appearing in the serums of both animals. One of the two dogs treated with heat-treated partially purified hog renin showed a moderate reduction in blood pressure whereas the other showed no change. Neither of these dogs showed antirenin. The two dogs treated with renal medulla extract showed no significant change in blood pressure. Antirenin developed in their serums in titre equal to that of the two dogs showing the slight antihypertensive effect from partially purified hog renal extract containing renin and equal to that of two dogs showing an excellent antihypertensive effect from a dialysis residue of partially purified hog renal extract containing renin.

We are now studying the possible antihypertensive potency of partially purified beef and sheep renal extracts containing renin. [This work was aided by grants from the John and Mary R. Markle Foundation, Parke, Davis & Company and the Graduate School Research Fund of the University of Illinois.]

**The influence of certain antispasmodics on postprandial intestinal activity.** K. G. WAKIM. *School of Medicine, Indiana Univ. Bloomington and Indianapolis.* The antispasmodic action of certain drugs led to their clinical usefulness in visceral and/or vascular spasms. Since their effectiveness is due to depression of smooth muscle tonus it is appropriate to investigate their effects on postprandial intestinal activity.

Trained dogs, with a previously prepared skin-covered intestinal loop, normally continuous with the rest of the gastrointestinal tract and with circulation and nerve supply intact, were used in

this study. With the dog lying quietly, a control tracing of intestinal motility was recorded kymographically by the use of an air-tight tambour system after which the animal was given the usual meal and the recording of intestinal activity was continued for one hour. At the end of the hour the drug to be studied was administered and its effects on postprandial intestinal activity were recorded. With the exception of amyl nitrite, which was given by inhalation, all the other drugs used in this study were administered intravenously.

Amyl nitrite, aminophylline, eotin hydrochloride, and trasentine inhibited intestinal activity and led to complete disappearance of peristalsis and rhythmical segmentation. The duration of the effect varied with the individual drugs administered. Demerol led to an immediate increase of intestinal activity for a period of about 5 minutes accompanied by defecation and then was followed by a period of complete cessation of intestinal activity lasting for a minimum of thirty minutes in every animal. Papaverine hydrochloride had practically no effect on intestinal activity.

This study indicates that the postprandial use of these antispasmodics, with the exception of papaverine, may delay intestinal activity.

The reversal and crystallization of a fibrous modification of insulin. DAVID F. WAUGH. *Dept. of Biology and Biological Engineering, Mass. Inst. Tech., Cambridge.* Crystalline insulin molecules may be united into fibrils having diameters of hundreds and lengths of thousands of Ångstrom units (Waugh. *Jour. Amer. Chem. Soc.* 66: 663, 1944). Evidence from filtration and attempted crystallization of suspensions of fibrils indicates that over 99 per cent of insulin present in a 2% solution may be converted into the fibrous form. Upon dilution with acid or distilled water, persistent flow double refraction replaces the initial static double refraction. In alkali (ca. 0.02 N), however, flow double refraction and viscosity decrease with time, indicating a disaggregation.

Crystallization of disaggregated material was accomplished as follows: 20 mg. of fibrous insulin was treated with 0.025 N NaOH at 0° for 18 hours. The isolectric precipitate obtained by neutralization was crystallized according to Romans, Scott, and Fisher (*Ind. Eng. Chem.* 32: 908, 1940). After 72 hrs. the crystals were found to have the same general cuboidal shape, density (between 1.31 and 1.325) and solubility in acid as native insulin. Analysis revealed 8 to 10 mgm. crystals, a recovery of 40% to 50%. Since the alkali treatment did not disaggregate all of the fibrils this amount is expected to represent a high proportion of the material actually reversed.

Apparently any molecular changes which accompany fiber formation are either insufficient to affect the crystallizing properties of the molecule

or the changes are *reversible*. During disaggregation the molecules revert to a form which crystallizes in the same way as native insulin.

Relation of the blood volume reduction to the mortality rates in experimental traumatic and hemorrhagic shock.<sup>1</sup> S. C. WANG, R. R. OVERMAN (by invitation), W. S. Root and M. I. GREGERSEN. *Dept. of Physiology, College of Physicians and Surgeons, Columbia Univ.* In order to determine whether or not the loss of blood could be the sole cause of death in traumatized dogs, our series of traumatic shock experiments was analyzed and the mortality rate compared with that of dogs suffering from simple hemorrhage. In the hemorrhage series, as in the traumatic shock experiments, a surgical anesthesia of 15 minutes duration was induced with ether, and a definite amount of blood was removed from the femoral artery. The blood volume of the animals was determined by the T-1824 dye method.

With a comparable residual blood volume after the insult the mortality rate in trauma is several times as high as that in simple hemorrhage. Traumatized animals rarely survived with a residual blood volume less than 68 cc. per kilogram body weight. On the other hand, most dogs survived a simple hemorrhage with a residual volume of only 58 cc. per kilogram body weight. When the data were analyzed statistically in the moving groups of 5 dogs, the residual blood volume at L.H. (lethal hemorrhage at 50 per cent mortality) in the simple hemorrhage series is 57 cc. per kilogram, while that in the muscle trauma is 71 cc. per kilogram. This difference in L.H. 50 values in the two series is statistically significant.

These observations provide a clear answer to a question of long standing, namely, whether or not the reduction in blood volume following muscle trauma is sufficient by itself to cause death. The evidence shows that additional factors (nervous?) are involved.

The recovery of skeletal muscle from the effects of partial denervation. W. H. WEHRMACHER (by invitation) and H. M. HINES. *Dept. of Physiology, State Univ. of Iowa, Iowa City.* Partial denervation of the rat's gastrocnemius muscle was accomplished by section of the fourth or fifth lumbar nerve or both. At designated times thereafter, determinations were made of muscle weight and isometric tension responses to direct and to tibial nerve stimulations. The muscle and nerve of the contralateral limb were employed as controls. In some experiments these controls were unoperated; while in others, lesions comparable to those in the experimental member were made 4 days before

<sup>1</sup> This work was done under a contract, recommended by the Committee on Medical Research, between the Office of Scientific Research and Development and Columbia University.

testing. The table lists the results in relation to the unoperated controls.

	Section response in percent of unoperated control	
	4 days post-operative	14 days post-operative
L <sub>4</sub> Section.....	67	80
L <sub>5</sub> Section.....	30	50
L <sub>4</sub> + L <sub>5</sub> Section.....	6	11

The greater strength response to nerve stimulation after the longer period of denervation was confirmed by direct comparison of the two sides of single animals which had a 4-day denervation on the one side and a 14-day denervation on the contralateral. Findings comparable to these in the rat were observed following section of L<sub>7</sub> in the cat. The relative improvement in the tension response of partially denervated muscle to nerve stimulation is not due to recovery from trauma and shock, regeneration of severed axons, or weakness induced in the control muscle. Hypertrophy of the non-denervated muscle fibers and extension or unmasking of peripheral neuromuscular terminals are considered to be possible factors in the recovery.

**Cardiovascular effects of a plasma substitute ("H.E.S. solution") in experimental hemorrhagic hypotension.<sup>1</sup>** GRACE E. WERTENBERGER and ROBERTA HAFKESBRING. *Dept. of Physiology, Woman's Medical College of Pennsylvania, Philadelphia.* The cardiovascular effects of intravenous injections of a hemoglobin solution ("H.E.S.") were studied in barbitalized dogs subjected to a posthemorrhagic hypotension period of 50 mm. Hg. for 30 minutes.

In 4 acute experiments, carotid pressure was held at 50 mm. Hg by initial rapid bleeding (average 5.3 cc./Kg./min.) and slow regulated bleedings. Total volume bled averaged 30 cc./Kg. and replacement averaged 85.5%. Injection rate was 2-3 cc./min. Electrocardiograms (Lead 2) were taken and hematocrit and hemoglobin determinations made at intervals. In 12 chronic experiments this procedure was repeated except that carotid pressures were not recorded.

In the acute experiments, mean arterial pressure was restored and satisfactorily maintained throughout the postinfusion period (3 hours). No secondary fall occurred. No electrocardiographic changes were noted except those characteristic of massive hemorrhage. These disappeared after infusion, though in some animals a second acceleration of rate appeared near the end of the observation period. Marked hemodilution occurred

during infusion and while a good degree of retention was evidenced a slight rise in the later hematocrit readings showed some trend toward hemodilution.

The chronic experiments gave similar results. All animals recovered and were in excellent condition when sacrificed at various intervals (1-22 days) for tissue studies.

Though irreversible shock did not develop in this short hypotension period, evidences of shock (subcutaneous petechiae, bloody intestinal fluid, etc.) appeared in seven animals.

Under these experimental conditions, the hemoglobin solution ("H.E.S.") proved an adequate plasma substitute effecting satisfactory hemodynamic recovery.

**The effect of inhalation of 100% oxygen on cardiac output in man.** W. V. WHITEHORN (by invitation), A. EDELMANN (by invitation), and F. A. HITCHCOCK. *Dept. of Physiology, Ohio State Univ., Columbus.* The cardiac outputs of normal men breathing 100% oxygen (Linde, U.S.P.) were estimated by means of the ballistocardiograph. Subjects were in the basal state in most cases, and in no case had food been ingested within 4 hours of the experiment. Records were obtained after a 15 minute control period of air breathing, and then at 15 minute intervals during the inhalation of 100% oxygen for periods up to 90 minutes. Control experiments in which air was breathed for the entire period were carried out.

Results indicate a diminished cardiac minute volume during oxygen inhalation. This decrease averages 12% of the control value after 15 minutes of oxygen breathing, and persists at about this level as long as oxygen is breathed. The decrease is statistically significant.

The decline in cardiac output is the result of the diminution in heart rate commonly seen during oxygen inhalation and also to a reduction in stroke volume. The relative importance of these two factors has not yet been established.

Further study of this response and its causes promises to provide valuable information with regard to the effects of 100% oxygen inhalation on circulation and its control.

**The effects of pulmonary overventilation and underventilation on brain potential.** G. C. WICKWIRE and RUTH KROUSE (introduced by W. E. Burge). *Dept. of Physiology, Univ. of Illinois, Urbana.* Overventilation was produced by vigorous, rapid and deep breathing for a minimum of 3 minutes. Mild tetany frequently resulted. Underventilation was brought about by inhibiting respiration to the maximum of voluntary effort.

When one platinum electrode was placed on the forehead and another on the forearm with a galvanometer in the circuit, the beam of light deflected an average of 8 divisions to the left of the

<sup>1</sup> Aided by a grant from the Foundation for Clinical and Surgical Research. Hemoglobin-Electrolyte-Stroma (H.E.S.) Solution supplied by Dr. John O. Bower of the Foundation.

zero line in 22 tests with 6 subjects, thus showing the forehead to be positive to the forearm. Each scale division represents 0.025 microamperes. Overventilation brought about an increased deflection of the beam of light to an average of 19 divisions to the left. Underventilation caused the light to deflect an average of 3 divisions to the right of zero. Readings taken by means of an electronic ohmmeter showed no variation in resistance with either overventilation or underventilation.

We have found that the scalp of lightly etherized dogs was positive when the underlying cortex was negative and that the positive potential of the scalp fluctuated with the negative potential of the brain cortex. Hence the increase in the positive potential of the forehead with overventilation indicated an increase of negative potential of the brain cortex. Similarly the decrease in positive potential of the forehead during underventilation indicated a decrease in negative potential of the brain cortex.

Plasma chloride and bicarbonate after administered potassium. WALTER S. WILDE and FREDERICK P. FERGUSON (by invitation). *Dept. of Physiology, School of Medicine, Louisiana State Univ., New Orleans 18.* According to Boyle and Conway an increase in extracellular potassium carries chloride and bicarbonate as the potassium salt from the extracellular fluid into muscle fiber water. Since the extracellular is the smaller volume, transfer of the anions yields mathematically larger, more directly determinable concentration changes in extracellular than in intracellular water (Wilde, Bull. Math. Biophysics 6: 105).

Nephrectomized dogs under amyta received intraperitoneally 500 mM  $\text{KNO}_3$ , 2.5 m Eq./kg. Whether after 2 or 4 hours' equilibration, the plasma Cl fell only 3.17 mM as the K rose 6.03 mM with insignificant correlation,  $\pm 0.465$ . The bicarbonate fell relatively more than Cl, probably in relation to the accumulating metabolic acids of nephrectomy. However in the first 2 hours the  $\text{HCO}_3$  fell so much as to suggest a special relation to the potassium injection. The measured loss of Cl from blood corpuscles, resulting from the Hamburger interplay between injected nitrate and lost bicarbonate, reduced the change in plasma Cl no more than 0.19 mM.

If the Cl lost from the estimated extracellular volume entered cell water as the potassium salt, this water amounted to only 17% of the body weight. Muscle fiber water represents 30%; the "apparent volume of distribution" of injected K included estimated cell water equal to 23% of the body weight. Instead of following Boyle and Conway concepts the chloride may have diffused into and been diluted by water attracted by the hypertonic  $\text{KNO}_3$  in the peritoneal cavity and elsewhere. Plasma sodium fell even more (5.9 MM).

The effect of sleeplessness on brain potential. MAUDE WILLIAMS (by invitation) and W. E. BURGE. *Woman's College, Univ. of North Carolina, Greensboro, and Univ. of Illinois, Urbana.* When one platinum electrode was placed on the forehead, and another on the forearm with a potentiometer in the circuit the forehead was found to be positive to the forearm with an average positive potential of 62 millivolts in 23 subjects. Remaining awake for 40 consecutive hours had no appreciable effect on the scalp potential while one or two hours of sound sleep immediately following the 40-hour sleepless period decreased the positive potential of the scalp to the zero level and caused in some instances a reversal in polarity.

We have found in etherized dogs that the scalp was positive and the underlying brain cortex negative, and that the positive potential of the scalp fluctuated in a 1 to 8 ratio with the negative potential of the brain cortex; so scalp potential may be used as an index to brain potential. Hence, the high positive potential of the scalp maintained during the 40-hour period of sleeplessness indicated a high negative potential of the underlying brain cortex, and the decrease to the zero level of the positive potential of the scalp during sound sleep immediately following the sleepless period indicated a fall during sleep in the negative potential of the brain cortex.

Water drinking by dehydrated men in desert environments. J. H. WILLS. *Depts. of Physiology and of Biochemistry and Pharmacology, School of Medicine and Dentistry, Univ. of Rochester, Rochester, N. Y.* The rates of drinking after rapid dehydration have been recorded during 23 tests on 11 men in the laboratory hot room and during 88 tests on 27 men in the desert. Such information is important in estimating the time required by dehydrated individuals to recover their usual contents of body water.

At the termination of dehydration in either the laboratory or the desert, men drink rapidly for the first 15 or 20 minutes. During this time they replace their total loss of water, if it is not greater than about 2 per cent of the initial body weight. It is possible that at higher levels of dehydration the factor preventing rapid satisfaction of the body's lack of water is the capacity of the stomach.

After the first 15 or 20 minutes of drinking, water ingestion proceeds more slowly than at first. Within 2 hours of the completion of desert marches, however, men who had walked without water reduced their deficits of body weight to about those of men who had water *ad libitum* during the marches (29 paired tests). Residual deficits are made up with meals.

Pilocarpine increased markedly the salivary flow of dehydrated men, but did not decrease drinking after dehydration. Aminophyllin, benzedrine and

caffeine also had insignificant effects on the amount of water taken during rehydration.

Cool water is the most preferred of all drinks for rehydration. Warm water, salted water (0.1 per cent NaCl) and flavored drinks were considered less palatable. (Work done under contract with the Office of Scientific Research and Development. Field Studies were made possible by various units of the U. S. Army.)

The bulbar olive in the cat. W. C. WILSON (by invitation) and H. W. MAGOUN. *Dept. of Anatomy, Northwestern Univ. Medical School, Chicago.* Cats in which one or both inferior olives were removed through a ventral parapharyngeal approach were observed into the chronic state. Terminally the midbrain tegmentum or bulbar reticular formation were electrically stimulated or the animal was anemically decerebrated.

Following loss of one olive (with inevitable partial retrograde degeneration of the other), the animals exhibited some body sway on standing, together with a hypermetria in the use of the contralateral legs most evident as a pronounced overflexion in gait. When tested free, the contralateral legs exhibited an extensor hypertonus occasionally associated with an overactive patellar reflex. As a result of a combination of these symptoms, the animals frequently fell to the side of the lesion when standing or walking. With bilateral lesions, hypermetria and extensor hypertonus were bilaterally present.

After unilateral olivectomy a myoclonus limited to the ipsilateral vocal cord occurred.

The characteristic tegmental response to midbrain stimulation was not altered by loss of one or both olives and therefore does not result from excitation of a midbrain-olivary pathway. Characteristic inhibitory effects from stimulating the bulbar reticular formation were also obtained in the absence of the olives.

The absence of one or both olives did not prevent the development of marked decerebrate rigidity.

Destruction and disappearance of brain stem neurons in guinea pigs receiving repeated concussion. W. F. WINDLE, H. M. SCHAMP (by invitation) and R. A. GROAT (by invitation). *Inst. of Neurology, Northwestern Univ. Medical School, Chicago.* Concussions were produced in guinea pigs weighting between 350 and 450 grams at intervals during a period of 3 to 7 weeks. Criterion of concussion was disappearance of the wink or eanthus reflex and production of a respiratory pause. Light chloroform or nembutal anesthesia was used and the control animals received the anesthetic.

The histopathology of concussion and postconcussion has been described previously (*Surg. Gynee. & Obstet.*, 79: 561, 1944). Principal alterations were found in the interneuron systems of the brain stem. Primary sensory and primary motor

neurons showed little or no effects of concussion. Blows administered repeatedly, led to diminution in the number of neurons in several nuclei of interneuron systems. This reduction amounted to as much as 40 per cent more of the large cells in such nuclei as Deiter's and the red nucleus. The large neurons of the pontile tegmentum were likewise diminished in number. Motor neurons of the facial nucleus were as numerous as in control animals. Some correlation between number and severity of blows and amount of cell destruction was apparent. [Work done under contract, sponsored by CMR, between OSRD and Northwestern Univ.]

Oral glucose tolerance in old age. R. WISOTSKY (by invitation), W. CORWIN (by invitation) and S. M. HORVATH. *The Metropolitan State Hospital, Waltham, Mass. and The Fatigue Lab., Harvard Univ.* Fourteen male patients normal in all respects except for their psychoses, between the ages of 60 and 70 years and living on a standard hospital diet, were subjected to oral glucose tolerance tests. They were given 0.75 grams of glucose per kilogram of body weight, an average intake of fifty grams per individual. Two to seven tests were performed on each subject at intervals of two to four weeks.

The glucose tolerance curves obtained exhibit wide variability not only between subjects but in the same subject. The following table presents the mean values for all the tests performed. The mean tolerance curves for the first and last tests on all individuals were also calculated but no significant differences were found.

*Mean blood sugar values of all glucose tolerance curves*

	Time									
	Fast-ing	$\frac{1}{2}$ hr.	$\frac{1}{2}$ hr.	$\frac{2}{3}$ hr.	1 hr.	$1\frac{1}{2}$ hr.	2 hr.	$2\frac{1}{2}$ hr.	3 hr.	
Mg %.....	124	162	205	219	221	220	188	156	128	

A decreased tolerance for glucose in aged males is indicated by these findings. This hyperglycemic curve is somewhat misleading since a number of the individual tolerance curves were definitely normal in character. However, both normal and frankly diabetic curves were observed on occasion in the same subject. Although the causes of these variations in oral glucose tolerance tests have not been explained fully, the inadequacy of a single tolerance test, especially in old age, is apparent.

Voluntary (self protective) maneuvers which can be used to increase man's tolerance to positive acceleration (motion picture).<sup>1</sup> E. H. Wood and G. A. HALLENBECK (by invitation). *Acceleration Lab., Mayo Aero Medical Unit, Rochester, Minn.*

<sup>1</sup> Work done under contracts with: (1) United States Army Air Forces, Wright Field, Dayton, Ohio, and (2) the Office of Scientific Research and Development, National Research Council, Washington, D. C.

Systolic blood pressure is a most important factor in determining man's tolerance to sudden exposure to high positive accelerations in the sitting position. Exposure to 5 grams for a duration greater than the symptom latent period of the retina or cerebrum to acute ischemic anoxia (3-10 seconds) usually produces blackout or unconsciousness. At this acceleration due to the height of the brain above the heart a systolic pressure of 120 mm. of mercury at heart level affords a systolic pressure of only 5 mm. of mercury at brain level and symptoms therefore result.

It has been found that voluntary maneuvers producing a temporary hypertension and aiding venous return will enable many individuals to maintain vision at 9 g. These maneuvers utilize either the pressor effect attained by coordinating muscular straining with a type of forced respiration or self-induced pressor reflexes such as occur immediately after a Valsalva maneuver of ten seconds' duration. Blackout prevention to 8 grams by one such maneuver (M-1) is illustrated. This maneuver is described to pilots as follows: "Just before the g comes on with all your strength pull your chin in and your shoulders up. Simultaneously push your belly against a tightly drawn safety belt as if straining at stool. As you do this, yell the word "Hey" as continuously as possible. Use up nearly all your breath on each "Hey", then grab a very fast breath and immediately start yelling again. Keep this up as long as you hold the g."

An analysis of factors involved in the protection afforded man by pneumatic anti-blackout suits.<sup>1</sup> E. H. WOOD, D. M. CLARK (by invitation) and E. H. LAMBERT (by invitation). *Acceleration Lab., Mayo Aero Medical Unit, Rochester, Minn.* Establishment of the sequence of physiologic events that occur in man during positive acceleration has allowed a quantitative and orderly approach to the problem of protecting the aircraft pilot against blackout. The problem becomes: How may this physiologic sequence be altered so that the period of progressive failure is reduced or eliminated? Inflatable bladder system suits have proved a convenient and effective means of accomplishing this in man. By the use of suits that allowed application of pressure to the legs, thighs, abdomen and arms separately and in combination, a quantitative analysis of the factors involved in the protection afforded by such suits has been made.

In general, as the pressure within the suits was raised, the protection afforded increased. The most important single factor in the amount of protection obtained was the amount of pressure applied to

the abdomen and trunk. In general, raising this pressure increased the protection afforded.

Application of pressure to the lower extremities alone afforded a barely perceptible amount of protection (average of 0.2 g). Pressure to the lower extremities, while providing little protection alone, was found to increase by a factor of (approximately) two the protection afforded by application of pressure to the abdomen.

The findings revealed the simplicity of the essential requirements for a simple, effective anti-blackout suit. They led to the development and use of a simple, uniformly pressurized bladder system, which may be built into any type of garment—be it underwear, trousers, coveralls, cutaway and so forth.

**Somatic sensory areas I and II of the cerebral cortex of the rabbit.** CLINTON N. WOOLSEY and GING-HSI WANG (by invitation). *Johns Hopkins Univ., School of Medicine, Baltimore 5, Md.* The "second" somatic sensory area described by Adrian (1941) as associated with claw mechanisms in *Felidae*, but present also in dog and monkey (Woolsey, *Fed. Proc.*, 1943; 1944), has been found in rabbit in Rose's cytoarchitectural area *Par. 5*. In this species it has been easy to show that the area receives impulses not only from limbs but also from face. (We have found since that this is true also for cat and monkey.) In fact, the area in each hemisphere, or in one hemisphere after ablation of the other, is activated by tactile stimulation of all parts of both sides of the body. Largest potentials are evoked by stimulation of face, limb apices and tail, smaller from more proximal parts of limbs, smallest from trunk. Contralateral responses are larger than ipsilateral ones. Deepening pentobarbital anesthesia suppresses ipsilateral responses first, those from contralateral face last. In rabbit there is much less spatial differentiation within somatic II than in the cat. Response areas for face, arm and leg largely overlap one another with their respective foci of maximal response separated by approximately 1 mm. Latencies are shorter in somatic area II than in somatic area I. Moreover, responses still occur in somatic II after removal of somatic I of the same hemisphere and somatic I and II of the opposite side.

The "primary" somatic sensory area (somatic I) has been mapped in terms of peripheral cutaneous areas. It is roughly coterminous with Rose's areas *Par. 1, 2, 3, 4 and Pc.*

**Influences of cortical areas upon the vestibulo-ocular reflex arc.** H. T. WRCIS (by invitation) and E. A. SPIEGEL. *Dept. of Exper. Neurology, Temple Univ. School of Medicine, Philadelphia, Pa.* The influence of various unilateral cortical lesions upon the ocular reactions to 10 alternate clockwise and counterclockwise rotations was studied in dogs and cats. Definite effects were found after occipital or

<sup>1</sup> Work done under contracts with: (1) United States Army Air Forces, Wright Field, Dayton, Ohio and (2) the Office of Scientific Research and Development, National Research Council, Washington, D. C.

frontal lobectomy, the postrotatory nystagmus to the operated side distinctly predominating over that to the normal side for one to seven days ("directional preponderance", i.e., increase in duration and number of jerks to the operated side and/or decrease to opposite side). Lesions of the parietal lobe or superficial temporal lobe lesions had only a slight, if any, effect upon the postrotatory nystagmus, while deep-reaching lesions of the latter lobe produced a definite directional preponderance, apparently due to injury of pathways connecting the area striata with the brain stem. After extirpation of one hemisphere, a definite

preponderance to the operated side was observed during the first week after operation and a slight difference in favor of this side for two more weeks. Unilateral frontal lobectomy following bilateral extirpation of the areae striatae results in no or only slight directional preponderance. The fact that severance of an optic tract or destruction of an external geniculate body have an effect upon the postrotatory nystagmus similar to that of cortical lesions (Spiegel and Scala, These Proceedings) suggests that the cortical influence upon the vestibulo-ocular reflex arc is part of a mechanism originating in the retina.

## THE AMERICAN SOCIETY OF BIOLOGICAL CHEMISTS

Abstracts of papers presented for the annual meeting scheduled for Cleveland, May 8, 9, 10, 1945. On account of the cancellation of this meeting, all the papers are to be regarded as "read by title". For possible correction in any of the abstracts see the next issue.

**The distribution of amino acids in normal adult male urine.** ANTHONY A. ALBANESE, L. EMMETT HOLT, JR., JANE E. FRANKSTON (by invitation) and VIRGINIA IRBY (by invitation). Dept. of Pediatrics, Johns Hopkins Univ., Baltimore. Experimental studies have led us to believe that significant information in regard to amino acid deficiencies and perversions of amino acid metabolism in disease can be obtained from a study of the amino acid excretion pattern in the urine. In order to evaluate abnormal patterns we undertook to study in detail the normal amino acid excretion pattern.

Urine specimens (24 hour) from 30 normal adult males (60-100 kg.) on normal diets were analyzed for 12 of the known amino acids by the application of known methods and those developed in this laboratory. The daily urinary amino-N was found to fall between 200- and 700 mg., which corresponds to 2.2 to 4.5 per cent of the total N. Calculations based on this data and the use of 136 as the average amino acid molecular weight indicate that from 1.9 to 6.7 grams of amino acids are excreted daily. The average distribution of the urinary amino acids in terms of amino acid N per cent of total amino N was found to be as follows:—arginine, 2.5; histidine, 9.4; methionine, 8.2; cystine, 1.3; tryptophane, 4.8; tyrosine, 4.7; phenylalanine, 9.4; valine, 12.0; leucine, 20.0; isoleucine, 0.0; hydroxy-amino acids, 0.0; undetermined amino N, 27.7. It is noteworthy that in no instance could isoleucine or the hydroxyamino acids be detected in these urines. This finding may be due in part to

the relatively low sensitivity of the tests for these particular amino acids.

**Fatigue effects in absorption.** JAMES C. ANDREWS and W. E. CORNATZER (by invitation). Dept. of Biological Chemistry and Nutrition, School of Medicine, Univ. of North Carolina, Chapel Hill. Comparisons of the rate of absorption of quinine salt from isolated intestinal loops of dogs have shown that equal doses, left in the loops for the same period of time, gave satisfactorily constant results for percentage absorption if administered at intervals of one or two days. However, if these doses are administered in rapid succession, the percentage absorption for the same periods of time drops rapidly. For these measurements standard doses of quinine dihydrochloride, equivalent to 20 mg. anhydrous quinine sulfate per kilo body weight, were used. The dose was left in the loop for 30 minutes. Immediately after washing out the unabsorbed residue another dose of the same size as that previously used was inserted. This procedure required a period of from 6 to 15 minutes, usually not over 10 minutes. The percentage absorption of the second dose averaged about 57 per cent of that of the first in the case of one dog and 74 per cent in the case of another. These results afford confirmation of our previous findings as regards the flattening of the curves of time versus percentage absorption when the results of separate experiments using different periods of time are plotted. A very definite fatigue effect is evidenced by both methods. [Supported by a grant from the Samuel S. Fels Fund.]

**Skeletal and soft tissue disuse atrophy in the rat.** W. D. ARMSTRONG. *Laby. of Applied Biochemistry, Univ. of Minnesota, Minneapolis.* An atrophy occurs of the bones of an extremity which is paralyzed or immobilized for a considerable time. If the disuse atrophy occurs as a result of a decreased rate of bone formation rather than from an increased rate of bone resorption, those factors which decrease the degree of bony disuse atrophy might rationally be used to accelerate the rate of fracture healing.

The nerves of the right brachial plexus were sectioned in mature male rats, and the animals were allowed to live 21 days following the operation. The weight of the skinned limbs, the dry, fat-free and the ash weight of the humeri were compared in operated animals fed an adequate diet (Group A—39 animals), animals fed a calcium deficient diet (Group B—32 animals), and in animals fed a phosphorus deficient diet (Group C—26 animals). The ash content of the right humeri of Group A was significantly less than that of the left humeri. This difference of ash content of the right and left humeri was increased in Groups A and B. The dry, fat-free weights of the humeri of the paralyzed limbs were lower than those of the left humeri by  $13.42 \pm 0.606$ ,  $26.05 \pm 0.608$  and  $23.03 \pm 0.746$  per cent, respectively, for Groups A, B, and C. The ash weights of the paralyzed humeri were lower than those of the left humeri by  $16.29 \pm 0.639$ ,  $29.96 \pm 0.636$  and  $25.85 \pm 0.851$ , respectively, for the three groups. [This work was supported by a grant from the Josiah Macy, Jr. Foundation.]

**Effects of lactose-containing diets on liver lipids.** CAMILLO ARTOM and WILLIAM H. FISHMAN (by invitation). *Dept. of Biochemistry, Bowman Gray School of Medicine, Winston-Salem, N. C.* Rats were maintained for 12 days on experimental diets in which lactose was substituted for sucrose or for both sucrose and dextrin. The liver lipids were analyzed and the results compared with those of controls on sucrose-dextrin containing diets. As expected, the control groups exhibited fatty infiltration and low lecithin levels in the liver. However, in the liver of rats on lactose substituted diets, much smaller amounts of neutral fat were found and also the lecithin levels usually were not as low as in the controls. The same results have been obtained with both low (10 per cent) and high (30 per cent) fat lactose-containing diets. Moreover, the effectiveness of choline supplementation in reducing the fat infiltration and in raising the lecithin level in the liver appears greater in animals maintained on lactose-containing diets.

Experiments have also been completed in which sulfasuccidine was added to lactose containing diets. In other experiments, various mono- and disaccharides have been substituted for carbohydrate

of the diet. [Aided by a grant from the John and Mary R. Markle Foundation.]

**A study of the relative toxicity of *l*- and *dl*-serine in rats.** CAMILLO ARTOM, WILLIAM H. FISHMAN (by invitation) and R. P. MOREHEAD (by invitation). *Dept. of Biochemistry and Pathology, Bowman Gray School of Medicine, Winston-Salem, N. C.* It has been previously shown that the administration by stomach tube of *dl*-serine (100 mg. daily) to rats on an experimental diet causes clinical symptoms (anorexia, loss in weight, albuminuria), leading to frequent deaths (often associated with signs of peripheral circulatory failure). The most characteristic pathological finding is the presence of severe necrotizing lesions in the renal tubules.

In the present study these experiments have been repeated on a small number of rats, employing the natural amino acid *l*-serine in place of the racemic mixture.

The administration of the amino acid was not accompanied by the clinical symptoms which had been observed with the *dl* mixture. Most striking was the complete absence of renal lesions.

It appears therefore that the unnatural *d* isomer is chiefly responsible for the injurious action of the racemic mixture. [Aided by a grant from the John and Mary R. Markle Foundation.]

**Pathological changes produced by a toxic component in *microcystis aeruginosa*.** C. T. ASHWORTH (by invitation) and M. F. MASON. *Dept. of Pathology and Experimental Medicine, Southwestern Medical College and Parkland Hospital, Dallas.* The pathological changes produced in rats following intraperitoneal administration of maximum sub-lethal doses of extract prepared from *microcystis aeruginosa* include a generalized cell damage with particularly severe injury of parenchymal liver cells. Cloudy swelling of the latter is observed as early as fifteen minutes after injection and this is followed by hydropic degeneration, fatty degeneration, and acute necrosis of the center of the lobules within three to four hours. The sinusoids at the center are markedly engorged with red blood cells, and the liver appears large, red and mottled on its surface due to dilated central vein areas. The dead liver cells disintegrate by autolysis, liberating cytoplasm into the circulating blood, and are removed within twenty-four to forty-eight hours. After forty-eight to seventy-two hours the liver is reduced in size, is yellow, and exhibits extreme fatty degeneration, collapse of liver lobules. The changes resemble in many respects those found in acute yellow atrophy. Regeneration is evident within three to five days and there is complete restoration of the lobule within thirty days. Hyperemia, acute parenchymatous and hydropic degeneration, fatty degeneration, and focal necrosis

are observed in the kidneys and to a lesser extent in the heart. Edema and hemorrhage occasionally occur in the lungs. Studies of effects of intermittent and chronic administration are in progress.

The electrophoretic mobility of human serum albumin as affected by lower fatty acid salts. G. A. BALLOU (by invitation) P. D. BOYER and J. MURRAY LUCK. *Dept. of Chemistry, Stanford Univ.* The purpose of this investigation was to study the possibility of association between serum albumin and simple non-polar anions. An hypothesis to this effect had been advanced by us to explain the effect of non-polar anions in increasing the thermal stability of human serum albumin.<sup>1</sup>

Solutions of human serum albumin, 0.5 percent, were equilibrated by dialysis against solutions of phosphate buffer (0.025 M total phosphate), fatty acid salt (up to 0.1 M, and enough sodium chloride to give a final ionic strength of 0.2. The pH in all cases was 7.7. The fatty acid salts studied were sodium butyrate, caproate, heptoate, and caprylate. The albumin mobility in the control sample was  $5.2 \times 10^{-6}$  em./sec/volt/cm.

Only in concentrations in excess of .08 M and .03 M, respectively, did butyrate and caproate increase the mobility of the albumin. In lower concentrations the mobility decreased. With both heptoate and caprylate the mobility of the albumin rose. The curve of mobility increase with caprylate passed through an inflection and rose sharply to attain a new maximum ( $6.6$  to  $6.8 \times 10^{-6}$  em/sec/volt/cm) with increase of caprylate concentration.

These results signify electrostatic association of the non-polar anion, R. COO<sup>-</sup>, with positively charged groups in the albumin molecule, increasing its net negative charge. This effect is dependent upon the specific affinity of the non-polar anion with the protein, and is greatest with caprylate. Experiments to explain the initial drop in mobility observed with butyrate and caproate are projected.

**Effect of thiouracil on the adrenal cortex, medulla and on the spleen.** EMIL J. BAUMANN and DAVID MARINE. *Montefiore Hospital, New York.* In addition to its effect on the thyroid, continued feeding of thiouracil brings about changes in many other organs. Among the more striking departures from normality are:

(1) Involution of the adrenal cortex which involves all three zones. There is extreme congestion that often results in hemorrhage in the reticular zone from which cysts may arise.

(2) There is a progressive increase in the size of the adrenal medulla that may amount to 50 per cent or more; because of the cortical involution, the medulla mass shows a much greater relative in-

crease. The cells take a deep chrome stain and the glands have a significantly higher adrenalin content than do normal adrenals.

(3) The spleen shrinks to  $\frac{1}{2}$  or  $\frac{1}{3}$  of its normal size. This shrinkage is confined largely to the pulp. Megakaryocytes are strikingly increased.

Deposits of thiouracil are often found in the kidneys and along the urinary tract with occasional complications that arise from these deposits. As feeding is continued, adaptation to the presence of thiouracil develops so that calculi, instead of growing, become smaller and disappear.

The change in the liver is predominantly a parenchymatous degeneration. In the gonads there are atresia of follicles and depression of spermatogenesis.

**The  $\beta$ -ketosteroid excretion of normal men.** EMIL J. BAUMANN and NANNETTE METZGER (by invitation). *Montefiore Hospital, New York.* Nearly all of the methods used for the estimation of 17-ketosteroids in urine are very inaccurate and the analyses reported are often grossly misleading. The main difficulty arises from the presence of interfering chromogens which investigators have been unable to remove by chemical means. In large measure we have overcome this difficulty by purifying urinary extracts by adsorption.

To establish standards of normality we report the total and  $\beta$ -17-ketosteroids of 60 normal men between the ages of 17 and 66. Although there is considerable variation among individuals in an age group, the average total 17-ketosteroid excretion is highest during the first part of the third decade, decreasing to 10 mg. per day or less after 30 years of age and to less than 6 mg. per day after 50.

The  $\beta$  fraction, which available evidence indicates arises from the adrenal cortex, usually makes up less than 0.5 mg. of the total except between the ages of 21 and 30. During this decade the excretion of  $\beta$ -17-ketosteroids rises, reaching a maximum of 4 or 5 mg. per day at 25-6, and in these cases this fraction may make up as much as 25 per cent of the total 17-ketosteroid excretion.

Among the subjects were 4 men who had healed gastric ulcers which had given no trouble for several years. All had low excretions for their ages and the  $\beta$  fraction was less than 0.5 mg. per day, although they were between 25 and 28 years old.

**Observations upon the formation, storage and excretion of creatine and creatinine in the rat in relation to phosphate and carbohydrate metabolism.** HOWARD H. BEARD and PHILIP PIZZOLATO (by invitation). *Dept. of Biochemistry, Louisiana State Univ. and the Charity Hospital, New Orleans.* Creatine-creatinine formation, storage and excretion in the rat have been studied from the standpoint of glucose and phosphate metabolism. The rat maintains his normal creatinine content of the muscles when fed on 5 as compared to 20 per cent

<sup>1</sup> Balou, G. A., Boyer, P. D., Luck, J. M., Lum, F. G., J. Biol. Chem. 153: 589, 1944; J. Clin. Investigation 23: 454, 1944.

protein checkers (Purina Mills, St. Louis). Under these conditions no increase in creatine formation occurred when 100 mg. each of arginine-glycine-methionine; urea-glycine-methionine; creatinine; or glycocystamine-methionine were injected in different studies. Due to a lack of available phosphate the increased creatine that was evidently formed was rapidly excreted into the urine. On the other hand the injection of either 50 mg. of calcium glycerophosphate or 300 mg. of glucose with each of the above supplements caused an increased formation and retention of creatine in the muscles.

It was concluded that the formation, storage and excretion of creatine, and to a lesser extent of creatinine, depend largely upon the amount of available phosphate in the tissues to hold creatine there as creatine phosphate. These results are in accord with our modern conception of the coupling of oxidations and phosphorylations in the body.

Further studies of the relation between creatine-creatinine metabolism and several body measurements. HOWARD H. BEARD and PHILIP PIZZOLATO (by invitation). *Dept. of Biochemistry, Louisiana State Univ. and Charity Hospital, New Orleans.* One hundred and forty-five rats varying in body weight from 50 to 400 gm. were divided into 7 groups in 50 gm. intervals. The actual body, muscle and skeletal weights were determined in each animal together with the per cent muscle creatine and the total creatine content of the muscles and the creatinine excretion. The correlation coefficient,  $r$ , between the different variables in the small groups was compared to the same values of  $r$  when the whole group of 145 rats was studied. Results were as follows:

On the average, 44 per cent of the body weight is present as muscle tissue, 8.6 per cent as skeleton, 0.2 per cent as total muscle creatine and the creatinine excretion was 11.35 mg. daily. The values of  $r$  between the different variables (body weight-muscle weight, body weight-total muscle creatine, muscle weight-skeleton) in the small groups were in most cases small and misleading, but the correlation between these same variables in the large groups was very significant,  $r = 0.72$  to  $0.96$ . The correlation between body weight and creatinine excretion taken from 39 studies from the literature was  $-0.54 \pm 0.07$ , showing that the larger the number of subjects the smaller the value of  $r$ , and the smaller the number of subjects the larger the value of  $r$ . No correlation was observed between the creatinine excretion of the rats and body weight, muscle weight, total muscle creatine, or per cent muscle creatine.

Further studies on the metabolic utilization of homocystine in the absence of known dietary methyl donors. MARY ADELIA BENNETT. *Lankenau Hospital Research Inst., Philadelphia.* Rats from this Institute have repeatedly grown on

the above diet with actual synthesis of methionine (Growth 8: 59, 89, 1944). These animals, pre-experimentally on an excellent diet, received eight B vitamins which, in addition to those from intestinal bacterial sources, enabled them to grow steadily for at least twenty days. Then reversible drops occurred accompanied by symptoms suggesting pantothenic acid deficiency. A "folic acid" concentrate (Williams, potency 5000) was fed to relieve these symptoms (cf. Wright and Welch, Science 97: 426, 1943). Negative results show that it is not the critical factor.

The addition of 2 per cent succinyl sulfathiazole to the homocystine diet, plus eight B vitamins, stopped the growth of these rats in approximately four weeks. Addition then to the eight B vitamins of (a) an extra 5 gamma biotin and 60 gamma of the "folic acid" concentrate, caused no resumption of growth (cf. Welch and Wright, J. Nutr. 25: 555, 1943), nor did (b) substitution of 50 mg. of Ryzamin B for the "folic acid" concentrate. However, replacement of homocystine by methionine resulted in growth which, on withdrawal of Ryzamin, stopped, with a decline in food consumption to zero. When (c) 100 mg. of Liver Extract Lilly was fed, in place of the B vitamins, to four rats from different litters, practically identical growths resulted, increasing to approximately 2 grams daily when the eight B vitamins were added to the extract. The methionine and choline contents of the extract do not account for the apparent methylation.

Carotene utilization by the guinea pig. LILLIAN S. BENTLEY (by invitation) and AGNES FAY MORGAN. *Laby. of Home Economics, Univ. of California, Berkeley.* A semi-purified vitamin A-free diet was devised which was satisfactory for production of vitamin A deficiency in guinea pigs in 3 to 4 weeks. Xerophthalmia, weight loss and early death occurred in these animals. Addition of beta-carotene or vitamin A to the diet cured the condition and permitted normal growth. Vitamin A, which was stored in the liver only, except for traces in the kidneys, was found in the liver in significant amounts only when massive doses, at least 2 mg. per kg. per day of beta-carotene were fed for 5 weeks. This is 16 times the amount reported necessary for other mammals. Liver storage occurred, however, on about 200 I.U. vitamin A per kg. per day. Depletion followed by vitamin feeding and a second depletion indicated that all reserves were exhausted in about 31 days when 10,000 I.U. of vitamin A had been fed, but in 21 days when an equivalent amount of carotene had been given. Another series of young guinea pigs fed fresh grass *ad lib.* were found to have 0.6 mg. vitamin A per liver but nearly all of this was lost in 15 to 30 days on the vitamin A deficient diet. Reproduction was more successful when vitamin A rather than caro-

tene was provided, abortions were fewer, survival of mothers and litters and liver storage of vitamin A were greater in the former case. [Aided by a grant from Swift and Co.]

**Synthesis of cholesterol by liver slices.** KONRAD BLOCH, ERNEST BOREK (by invitation) and D. RITTENBERG. *Dept. of Biochemistry, Columbia Univ., New York.* The synthesis of cholesterol in intact animals involves condensation of molecules of small size. Deuterium is incorporated into cholesterol when either rats or mice are given D<sub>2</sub>O or isotopic acetic acid. (*Jour. Biol. Chem.* 121: 235 (1937); 145: 625 (1942).) We have now demonstrated the synthesis of cholesterol by surviving liver slices.

Liver slices from young rats were incubated in a Krebs-Phosphate buffer to which either isotopic acetate or D<sub>2</sub>O had been added. After incubation for three hours cholesterol was isolated and found to contain high concentrations of deuterium. Synthesis of cholesterol took place aerobically only; it was within wide limits independent of acetate concentration. The cholesterol contains heavy carbon when acetic acid labelled with C<sup>14</sup> is used. It is estimated that cholesterol is synthesized by liver *in vitro* at a rate similar to that *in vivo*. These results establish the liver as one of the sites of cholesterol synthesis.

Smaller but significant concentrations of isotope were found in the fatty acids isolated from the same experiments. Again, negative results were obtained under anaerobic conditions.

**Further observations on the trypsin retarding fractions of navy and other beans.** DONALD E. BOWMAN. *Dept. of Biochemistry and Pharmacology, Indiana Univ. School of Medicine, Indianapolis.* The alcohol insoluble, trypsin retarding fraction which can be obtained from aqueous extracts of navy beans following isoelectric precipitation of the bean proteins can be further concentrated by precipitating remaining proteins with trichloroacetic acid. The active material present in the fraction which can be reprecipitated with alcohol from such filtrates is relatively stable in subsequent aqueous solution.

Trypsin retarding properties also characterize simple aqueous extracts of Georgia velvet beans and white Chinese velvet beans. Both the alcohol and acetone precipitates of such extracts exhibit some antitryptic properties. Although a large part of the antitryptic activity originally present in aqueous extracts of soy beans is lost by alcoholic precipitation such extracts contain a trypsin retarding fraction which can be repeatedly reprecipitated with alcohol.

As one of the first steps in an investigation of the influence which these fractions might have upon the manifestations of trypsin shock or parallel states simultaneous injection with intravenously

administered trypsin has been followed. The fall in blood pressure which is caused by commercial trypsin was not prevented by the navy and soy bean preparations thus far employed and under the conditions which prevailed.

The navy bean preparations show a definite tendency to retard the destruction of erythrocytes by trypsin *in vitro* when enough of the latter is used to establish a moderate rate of hemolysis. With larger amounts of trypsin the influence is less apparent. Additional observations deal with the influence on trypsin toxicity, and bacterial proteolysis and other properties.

**Iodination of aniline and thiouracil in vitro.** DONALD E. BOWMAN. *Dept. of Biochemistry and Pharmacology, Indiana Univ. School of Medicine, Indianapolis.* A study of substances, other than those of a phenolic nature, which might be capable of utilizing iodine *in vitro* at increased rates at moderately elevated temperatures and in the presence of sufficient relative amounts of a salt such as a phosphate buffer, has shown that aniline and thiouracil can be included in this group.

Very decided increases in the reaction rates of dilute solutions of aniline or related substances are apparent in the presence of sufficient relative amounts of phosphate at body temperature. Such properties are shared by p-aminobenzoic acid and related substances such as sulfaguanidine and sulfanilamide when the latter are used in somewhat larger amounts relative to the iodine. Within limits, the degree of such increases in reaction rates vary directly with relative increases in phosphate concentrations. Citrate has a similar influence.

Increases in pH levels, maintained on the acid side of neutrality in the present study, favors the reaction rate.

In comparison with tyrosine or aniline, thiouracil shows less dependence upon salt concentration, temperature and pH, reacting with iodine more rapidly in certain instances than does either tyrosine or aniline. Moderate reductions in temperature below that of the body retards the iodination of tyrosine more than that of thiouracil.

The relation between these observations and the physiological characteristics of these substances bears further investigation.

**The effect of sodium citrate on the absorption, excretion and toxicity of sulfathiazole.** JEAN BURRELL, JACK R. LEONARDS and ALFRED H. FREE (introduced by Victor C. Myers). *Dept. of Biochemistry, School of Medicine, Western Reserve Univ., Cleveland.* The administration of alkali along with the sulfonamide drugs often has been advocated and employed as a measure of preventing crystallization of the drug in the kidneys. The present study was undertaken to determine whether the physiological alkali, sodium citrate, had any other effects on the metabolism of sulfathiazole.

The citrate and sulfathiazole were administered together in the form of a standard effervescent tablet which yielded 0.5 gram of sulfathiazole and 2.0 gm. of sodium citrate. These proportions were adhered to in all of the experiments.

The rate of absorption in rats was determined directly by sacrificing the animals one hour after the oral administration of the sulfathiazole and analyzing for the unabsorbed sulfathiazole remaining in the gastrointestinal tract. The rate of intestinal absorption was found to be 10.5 mg. per 100 gm. of body weight per hour. The simultaneous administration of sodium citrate had no appreciable effect on the rate of absorption of sulfathiazole.

The blood level of sulfathiazole was determined at regular intervals following the oral administration of the drug to dogs and to normal human subjects. Experiments carried out a week later on the same subjects indicated that the blood levels and rate of urinary excretion of sulfathiazole were similar if the drug was given alone or together with sodium citrate.

Preliminary studies indicate that large doses of sulfathiazole (1 gm./kg./day for 80 days) or sulfathiazole-citrate mixtures had no demonstrable toxic effects in rats.

**Vitamin B<sub>6</sub> (pyridoxine) and granulocytopenia.** MAX M. CANTOR and JOHN W. SCOTT (introduced by G. Hunter). *Depts. of Biochemistry and Medicine, Univ. of Alberta, Edmonton.* Vitamin B<sub>6</sub> (Pyridoxine) was administered to normal adults and to patients with leucopenia and, or granulocytopenia. Some of these were cases of agranulocytic angina which developed following the administration of sulfathiazole or thiouracil. The blood changes in others were those commonly found in infectious mononucleosis, lupus erythematosus and aleukemic leukemia. Apart from a transient rise in the level of monocytes in the blood, there was no change in the blood picture of normal adults. Patients with toxic granulocytopenia showed a rapid and sustained elevation in the white cell count and a marked increase in granulocytes. The patients with infectious mononucleosis responded in the same way as normal persons. The response in lupus erythematosus and in aleukemic leukemia was similar to that found in toxic granulocytopenia. It is concluded that pyridoxine is the factor involved in the "maturation" of the polymorphonuclear leucocyte and specifically stimulates granulocytopenia.

**The excretion of pyrimidine and thiamine by man in different nutritional states.** W. O. CASTER (by invitation), H. CONDIFF (by invitation), OLAF MICKESEN and ANCEL KEYS. *Laby. of Physiological Hygiene, Univ. of Minnesota, Minneapolis.* Three groups of young men were maintained for 6.5 months on identical diets, but adjusted with pills to constant total thiamine intakes of 0.6, 1.0

and 1.8 mg. per day, respectively. At various times the subjects consumed diets high in carbohydrate, protein and fat, and underwent a 3-day fast accompanied by hard work.

The urinary excretion of pyrimidines in terms of 2-methyl-5-ethoxymethyl-6-amino pyrimidine (estimated by a modified fermentation method) was found to be qualitatively similar to that of thiamine. After a few weeks the thiamine excretions tended to stabilize at zero, at 0.025 and at 0.200 mg. daily for the respective 3 groups. The corresponding pyrimidine excretions were 0.100, 0.160 and 0.260 mg. daily. The excretion of both thiamine and pyrimidine decreased markedly in starvation, increased during the high fat diet, and showed no change during the high protein or high carbohydrate diets.

After 6.5 months the thiamine intake of all the subjects was reduced to zero. Within a few days the thiamine excretion was zero for all subjects. The pyrimidine excretion throughout this period decreased continually, but even after 4 weeks when marked symptoms of acute thiamine deficiency were present, there were easily measurable amounts of pyrimidine in the urine. At the end of this regimen, the pyrimidine excretions increased more rapidly than the thiamine excretions. [This work was supported in part under the terms of a contract between the Regents of the Univ. of Minnesota and the Office of Scientific Research and Development. Support from other sources will be acknowledged in final publication.]

**A growth factor for *Lactobacillus gayoni*.** VERNON H. CHEDLEIN, THOMAS RIGGS and HERBERT P. SARETT (introduced by Robert R. Williams). *Dept. of Chemistry, Oregon State College, Corvallis.* In contrast to all species of lactic acid bacteria studied thus far, *Lactobacillus gayoni* 8289 fails to grow or produce acid on a medium containing glucose, salts, hydrolyzed casein, charcoal treated peptone, Lloyd's reagent treated yeast, cystine, tryptophane, adenine, guanine, uracil and all known B vitamins. Good growth and acid production can be obtained by addition of peptone or yeast and liver extracts.

The growth promoting activity of these substances cannot be replaced by various amino acids, purines, pyrimidines, nucleic acid (or its hydrolytic products), folic acid (Williams), *L. casei* factor (Stokstad), glutathione or coenzyme I. The behavior of the growth principle toward various reagents is different in one or more respects from that of the tomato eluate factor and vitamins B<sub>c</sub>, B<sub>10</sub> and B<sub>11</sub>.

The *L. gayoni* factor is liberated most effectively from fresh liver by enzymatic digestion. It is stable to mild acid hydrolysis, but is destroyed more rapidly by alkali. It is adsorbed by charcoal or Lloyd's reagent from acid solutions, is precipitated

by several heavy metal ions and by high concentrations of organic solvents.

Experiments are in progress on concentration and further characterization of this factor.

**Dietary factors and control of glycosuria in experimental pancreatic diabetes.** WALTER E. CISZEWSKI (by invitation), JAMES C. MATHIES (by invitation) and O. H. GAEBLER. *Dept. of Laboratories, Henry Ford Hospital, Detroit.* In experiments on 3 depancreatized dogs, extending over a period of 18 months, the authors attempted to determine whether water soluble vitamins affect the insulin requirement. A diet of casein, cracker meal, corn oil, calcium phosphate, salt mixture, and haliver oil was used. The food intake was constant, for experiments were terminated if anorexia developed. To provide pancreatic enzymes and lipocaine, 15 gm. of pancreatin was fed daily. The diet was completed by addition of yeast, and the minimal dose of insulin required to control glycosuria was determined. Effects of withdrawing yeast from the diet and replacing it, or substituting various combinations of thiamine, riboflavin, nicotinic acid, pyridoxine, pantothenate, and inositol, were then studied by observing the nitrogen balancee, glucose excretion, blood sugar curve after meals, blood fat, and urine ketones.

In a considerable number of experiments, but not invariably, progressive glucosuria began about 15 days after withdrawal of yeast. Ultimately 50 to 70 gm. of glucose were excreted daily. These amounts about equalled the starch content of the diet. In those experiments in which dietary deficiency caused losses of weight and nitrogen, the additional catabolism of protein was a negligible source of glucose. The glycosuria disappeared in 6 days if yeast feeding was resumed, or if all the pure vitamins mentioned above were fed. It could also be controlled by increasing the insulin dose. Its appearance was delayed, but not always prevented, when adequate amounts of thiamine, riboflavin, and nicotinic acid were given.

**Effect of vitamin E and tryptophane-deficient diets on storage of vitamin A by rats.** S. W. CLAUSSEN, A. B. McCOORD (by invitation) and B. L. GOFF (by invitation). *Dept. of Pediatrics, Univ. of Rochester School of Medicine, Rochester, N. Y.* One hundred and twenty rats, 3-4 weeks old, received a diet free of tryptophane and vitamin A. Sixty rats received the same diet with tryptophane. All had received the same amount of vitamin A before the experiments began. One half in each group were given 0.5 mg. mixed tocopherols in 2 drops of olive oil each day, and the remainder 2 drops of olive oil each day.

The rats which received the diet with tryptophane grew well (sacrificed after 42 days). The male rats which had been given vitamin E grew more rapidly than their controls which had received no

vitamin E while the reverse was true for the female rats.

The mean amount of vitamin A in the livers of these male rats which had received vitamin E was 302 Evelyn Units and of the female rats 381 E. U., while for the rats which received no vitamin E, the values were 244 and 314 respectively. One Evelyn Unit equals about 3.8 International Units of vitamin A.

The mean time of survival of the male rats given the tryptophane-free diet and vitamin E was 45.4 days, and of the female rats, 54.0 days, while the values for the groups which did not receive vitamin E were 45.2 and 54.3 respectively. The mean amount of vitamin A in the livers of these male rats given vitamin E was 116 E. U., and of the female rats, 130 E. U., while the values for the male and female rats not given vitamin E were 137 and 147 respectively.

**Antihemolytic value of the blood to lysolecithin in various conditions.** H. B. COLLIER, C. B. WELD and K. M. WILBUR (by invitation). *Depts. of Biochemistry and Physiology, Dalhousie Univ., Halifax, N. S.* The antihemolytic value (AHV) of the blood was measured by the method of Collier and Wilbur (*J. Lab. Clin. Med.* 29: 1123, 1944). When fat was given by mouth to cats and dogs, and oleic acid to dogs, the resulting lipemia was accompanied by little or no change in the AHV of the plasma. Decrease in the opacity of lipemic plasma following heparin injection also left the AHV unaltered. Intravenous injection of emulsified oleic acid (30 mg. per kg. in the dog) caused a slight but definite decrease in the AHV of cells and of plasma.

In phenylhydrazine anemia in rabbits there was a marked decrease in the AHV of the erythrocytes, accompanying a decreased resistance to hypotonic hemolysis.

In a small number of cases of secondary anemia in humans, the AHV of the erythrocytes was normal. The AHV of the whole blood was generally higher than normal, due to the high ratio of plasma volume to cell volume.

**A tracer study of iron metabolism with radioactive iron. I. Methods: absorption and excretion of iron.** D. HAROLD COPP (by invitation) and DAVID M. GREENBERG. *Division of Biochemistry, Univ. of California Medical School, Berkeley.* The radioactive isotope of iron, Fe<sup>55</sup>, prepared by deuteron bombardment of manganese, with a high specific activity, was employed in a study of iron metabolism in the rat. To measure its weak radiations, the iron was first electroplated, and the radiations were measured with a mica window Geiger counter tube. A dose of 0.05 mg. of this radioactive iron (with a specific activity of 0.5 to 2 microcuries per mg.) was administered as the neutral citrate to normal rats maintained on a stock diet, and to anemic rats which had been rendered iron deficient

by being reared on a diet of powdered milk. The animals were sacrificed at intervals up to four days and were rendered blood free by a simplified method of viviperfusion. Tissues and excreta were wet ashed, and the total iron in each sample was determined colorimetrically with o-phenanthroline.

Orally administered Fe\* was absorbed rapidly and was efficiently utilized by anemic iron deficient rats, over 90 per cent appearing in the blood within four days. Absorption apparently took place from both large and small intestines. In contrast, the normal animals absorbed only a small part of the iron dose.

When the radioactive iron was administered parenterally, less than two per cent was excreted in urine and feces in the first four days, with insignificant amounts in the bile. This limited excretion of iron emphasizes the importance of absorption in regulating the iron stores of the body.

A tracer study of iron metabolism with radioactive iron. II. Utilization and storage. D. HAROLD CORR (by invitation) and DAVID M. GREENBERG. *Univ. of California, Berkeley.* The turnover of radioactive iron in the various tissues of the rat was determined following intraperitoneal injection of a small dose (0.05 mg. Fe\*) as neutral citrate.

The rate of turnover was most rapid in the bone marrow, half of the accumulated Fe\* disappearing within 12 to 48 hours. This was reflected in the speed with which the "tagged" iron appeared in the hemoglobin of the blood, the rate being taken as an index of the bone marrow activity. Increase bone marrow activity was demonstrated thus in anemic iron deficient rats, especially when copper was also given; in adult rats receiving polycythemic doses of cobalt; in adult animals five days following severe blood loss; and in young growing rats as compared to adults.

The liver was found to have an important function in iron storage, with the spleen playing only a minor role. A few hours after intravenous or intraperitoneal injection of radioactive iron a large part of the dose was stored temporarily in the liver. Much of this excess liver Fe\* was utilized in hemoglobin synthesis within the next few days. The amount stored in the liver was much less when the Fe\* was injected subcutaneously or administered orally with slower absorption and a correspondingly small rise in the level of serum iron. It was also greatly reduced when the Fe\* was being rapidly used for hemoglobin synthesis by bone marrow stimulated by cobalt treatment, blood loss, or iron deficiency anemia.

Methionine determination in proteins and foods. FRANK A. CSONKA and CHARLES A. DENTON (by invitation). *Agricultural Research Administration, U. S. Dept. of Agriculture, Washington.* The use of the spectrophotometer in the estimation of methionine by the sodium nitroprusside reaction of

McCarthy and Sullivan was investigated. The color obtained by this reaction showed a minimum transmission at 510 m $\mu$ . When the reaction was carried out with pure methionine a stoichiometric relationship of 2 parts of nitroprusside to 1 part of methionine was demonstrated. However, when glycine was added or the reaction carried out with a protein hydrolysate this relationship was not valid. The addition of glycine changed the transmission percentage of the nitroprusside reagent. For example, 20 mgs. of nitroprusside in a blank gave 70 per cent transmission at 510 m $\mu$ , whereas in the presence of 10 mgs. of glycine the percentage transmission was 84. In addition to this effect, the presence of glycine also reduced the intensity of the color formed by the methionine-nitroprusside reaction. When 1 mg. of methionine and 2 mgs. of histidine were present in the reacting mixture, the color produced by the histidine was only partially discharged by 10 mgs. of glycine. However, the color produced by 1 mg. of histidine in the presence of methionine is totally discharged by 10 mgs. of glycine. Therefore, the quantity of histidine present in the test solution should be limited to 1 mg. or less. The use of mercuric salts for separating amino acids from the humin and other materials in a protein hydrolysate proved successful.

Chemical changes in dietary chloride deficiency in the rat. ELIZABETH M. CUTTERBERTSON (by invitation) and DAVID M. GREENBERG. *Univ. of California Medical School, Berkeley.* Rats (males) reared on a synthetic diet containing only 2 to 5 mg. of chloride per 100 gm. of food plateaued in weight at 130 gm., whereas the controls reached levels of 400 gm. On paired-feeding, the controls gained twice as much as the deficient pair-mates, indicating inefficient utilization of food by the latter.

Despite close conservation of chloride by the deficient animals, the chloride in the blood serum was reduced from 104 mM to 70 mM per liter. Perhaps as a partial compensation, the carbon dioxide content (whole blood) was increased from 25.8 to 32.3 mM per liter.

Analysis showed a considerable reduction in the chloride content of skin, muscle, kidney, liver, testes, stomach, lung and brain, but there was a significant increase in the heart. Calculation of the extracellular fluid volume from serum and tissue chloride values or by the distribution of radioactive sodium showed that the chloride and sodium spaces were consistently increased in most of the tissues and in the body as a whole, of the chloride deficient rats.

Chloride deficiency, because of the induced alkalosis, is accompanied by a twenty-fold increase in urinary citrate excretion; from 0.5 to 1.5 mg. 10 to 30 mg. per rat per day.

The deficiency produces extensive kidney damage, beginning in the convoluted tubules and even-

tually involving the whole nephron, which may then be replaced with connective tissue. The degeneration begins very shortly after the rats are put on the deficient regimen.

**Crystalline human hemoglobin and myoglobin. Standardization of the hemoglobins and denaturation studies.** DAVID L. DRABKIN. *Dept. of Physiological Chemistry, School of Medicine, Univ. of Pennsylvania, Philadelphia.* Parallel studies have been carried out upon the crystalline hemoglobins and myoglobins of horse, dog and man. The pigments of the human species have been crystallized successfully in a form suitable for crystallographic characterization. Human hemoglobin belongs to the tetragonal system (habit, bipyramidal), and the myoglobin is orthorhombic.

A procedure for standardization of the hemoglobins and myoglobins is proposed. It is based upon the interchangability of the spectrophotometric constant at 540 m $\mu$  of the cyanide derivatives of the ferric forms of the hemoglobins, myoglobins and protoporphyrin (from which a gravimetric standard can be prepared). The concentration of the hemoglobins and myoglobins can be obtained photometrically by comparison of aliquots converted to cyanmethemoglobin against a standard of hemin-dicyanide, or against a standard of cyanmethemoglobin, whose concentration is based upon the determination of N in salt free solutions prepared from blood corpuscles.

Myoglobin, as judged spectrophotometrically by conversion to hemochromogen, is unusually stable towards alkali (pH 13 to 14) in comparison with hemoglobin. The writer has demonstrated (Proc. Soc. Exper. Biol. and Med. 41: 225, 1939) that 4M urea accelerates 60-fold the rate of denaturation of hemoglobin by alkali. It is now found that 4M urea produces a remarkable increase (1000-fold) in the rate of alkaline denaturation of myoglobin. In the presence of urea the alkali resistant myoglobin, whose molecular weight is only 16,700, is as rapidly converted to hemochromogen as the easily denatured 66,700 unit of hemoglobin.

**The structure of the antibiotic, aspergillie acid.<sup>1</sup>** JAMES D. DUTCHER (by invitation) and O. WINTERSTEINER. *Division of Organic Chemistry, Squibb Inst. for Medical Research, New Brunswick, N. J.* In a preliminary report<sup>2</sup> evidence was presented on the basis of which a structure (I) was proposed for this antibiotic agent. The present paper reports further observations on the chemical behavior of this product and other confirmatory evidence for the designated structure.

Treatment of aspergillie acid with bromine-water yielded 5-bromoaspergillie acid. The bacteriostatic

potency of this compound was measured by G. Rake and H. P. Jones of this Institute against *Streptococcus hemolyticus* C203. The freshly prepared solution showed an activity 8 to 10 times as great as aspergillie acid itself. This appears to be the first reported instance of the modification of the structure of a natural antibiotic agent to increase its activity substantially.

Further confirmation of the structure of desoxyaspergillie acid (II) was obtained through the following reactions: 1. With bromine in acetic acid a perbromide,  $C_{12}H_{20}ON_2 \cdot HBr \cdot Br_2$ , was formed. 2. Treatment with methyl iodide yielded a crystalline methiodide,  $C_{13}H_{22}ON_2I$ . Exhaustive methylation failed to cleave this ring system. These reactions are characteristic of pyrazine derivatives.<sup>3</sup>

In addition to the previously reported preparation from isoleucine anhydride of 2,5-di-sec. butyl-piperazine, a reduction product of aspergillie acid, the synthesis of this product has been accomplished by an independent route via the corresponding pyrazine.

**The form and amount of morphine excreted in relation to size of dose.** ANNA J. EISENMAN. *Research Dept., U. S. Public Health Service Hospital, Lexington.* In the preliminary experiments, increasing doses of morphine sulfate were given to human post-addicts and the first and second urine voidings were analyzed. The results indicated that, in general, free morphine does not appear in the urine before the third hour. Detectable amounts of bound morphine appeared during the first twenty minutes.

In the second set of experiments, four subjects were given 20, 30, 40 and 60 mg. of morphine sulfate at fortnightly intervals. Urine was collected at one hour, at three or five hours, and at 24 hours. Since the three hour specimens after the 20 and 30 mg. doses failed to show free morphine, the second collection interval for the 40 and 60 mg. experiments was set at five hours. Three hour values exceeded the 0.5 mg. allowed for a blank but the results are the sum of two analyses neither of which exceeded 0.5 mg. About 2 mg. of free morphine was excreted after five hours. For the 24 hour specimens the amount of free morphine bears no constant relation to the total amount excreted or to the dose of morphine. The ratios of total morphine to dosage vary inversely as the dosage, e. g., 65 per cent for 20 mg. vs. 43 per cent for 60 mg. This may explain why a 60 mg. dose of morphine is not three times as effective as a 20 mg. dose. There is a slight decrease in urine volume with increasing amounts of morphine.

**Anaerobic glycolysis of brain suspensions.** K. A. C. ELLIOTT and MARYON HENRY (by invitation).

<sup>1</sup> White, E. C. and J. H. Hill. *J. Bact.* 45: 433, 1943.

<sup>2</sup> Dutcher, J. D. and O. Wintersteiner. *J. Biol. Chem.* 155:

359, 1944.

Treadwell, F. *Ber.* 14: 1465, 2161, 1881.

Stoehr, F. J. *pr. Chem.* (2) 47: 463, 1893.

Aston, J. G. *J. Am. Chem. Soc.* 52: 5254, 1930.

*Inst. of the Pennsylvania Hospital, Philadelphia.* Dilute suspensions of rat brain, prepared in Ringer-bicarbonate-glucose, glycolyse at a rate comparable with that of slices and the results are much less variable. The rate of glycolysis of the tissue suspensions is increased by the presence of traces of oxygen, by centrifuging and washing with isotonic medium, and to some extent by previous aerobicosis. The rate is decreased by increasing tissue concentration, by extract from strong suspensions, by serum, and to some extent by spinal fluid.

Pyruvate in  $5 \times 10^{-8}$  molar concentration gives maximum stimulation. Stimulation by traces of oxygen, or by previous aerobicosis, is accounted for by the traces of pyruvate formed and maintained in the slight aerobic metabolism of glucose. The stimulation by washing is due to the removal of factors which destroy pyruvate. Inhibition by tissue extract is due to the presence of these factors. The effect of increased tissue concentration is partly due to these factors and partly due to another inhibitor. Inhibition by serum is not due to pyruvate destruction.

Mg has little effect on plain suspensions but stimulates glycolysis when pyruvate is added. The stimulatory effect of washing occurs only when Mg is present. Lactic acid inhibits appreciably in the absence, but not in the presence, of added pyruvate. Preliminary aerobic incubation without glucose for 20 minutes causes 85 per cent destruction of glycolytic activity; if traces of oxygen are present incubation without glucose has much less effect. [Aided by a grant from the Committee on Therapeutic Research, Council on Pharmacy and Chemistry, American Medical Association.]

**Respirations of brain suspensions at low oxygen tensions.** K. A. C. ELLIOTT and MARYON HENRY (by invitation). *Inst. of the Pennsylvania Hospital, Philadelphia.* When the metabolism of tissue slices is studied at low oxygen tensions the results reflect a mixture of aerobic metabolism of superficial cells, anaerobic metabolism of inner layers, and intermediate conditions. It has been shown (*J. Biol. Chem.* 143: 227 1942) that brain suspensions prepared in isotonic glucose-containing medium respire about as rapidly as slices, and their respiration rate is scarcely affected by the dilution of the suspension. In such suspensions the particles are small enough to allow the assumption that all parts of the tissue are subjected to the same low oxygen tension. With sufficiently dilute suspensions, the rate of diffusion of oxygen from the gas phase into the medium does not limit the oxygen uptake. By using tissue concentrations as low as 4-8 mg. per cc., it has been found that brain suspensions respire at the same rate as in air or oxygen when the oxygen tension is reduced at least as low as 0.4 mm. Hg (respirometers filled with ordinary commercial nitrogen). As the tissue concentration is raised, or

as the oxygen tension is reduced by respiration, diffusion of oxygen into the medium becomes slower than the rate of utilization and the effective O<sub>2</sub> tension in the medium falls. Then respiration per unit weight decreases while glycolysis increases toward a maximum, being stimulated by the traces of pyruvate produced by the slight aerobic metabolism. At still higher tissue concentrations glycolysis per unit weight decreases again as a result of inhibition by tissue extractives. [Aided by a grant from the Committee on Therapeutic Research, Council on Pharmacy and Chemistry, American Medical Association.]

**Biochemistry of the malarial parasite, plasmodium gallinaceum.** E. A. EVANS, JR., JOSEPH CEITHAML (by invitation), JOHN F. SPECK (by invitation) and JAMES W. MOULDER (by invitation). *Dept. of Biochemistry, Univ. of Chicago.* The erythrocytic forms of *P. gallinaceum* afford a convenient system for the study of the metabolism of the malarial parasite.

Washed suspensions of parasitized chicken erythrocytes oxidize glucose with the intermediate formation of lactic and pyruvic acids. Significant quantities of the glucose used by this organism cannot, as yet, be accounted for.

Under anaerobic conditions, the organism quantitatively converts glucose into lactic acid. By use of cell-free extracts, it has been demonstrated that the parasite splits glucose into lactic acid by means of a phosphorylating glycolysis similar to that of mammalian muscle.

During the utilization of glucose by the plasmodium, intracellular protein (hemoglobin) is broken down. This proteolysis is apparently coupled with the aerobic utilization of glucose. Cell-free extracts which hydrolyze hemoglobin have been obtained from *P. gallinaceum*.

The oxidation of lactic and pyruvic acids by erythrocyte-free parasite suspensions is catalyzed by small amounts of fumaric acid and is inhibited by malonic acid. It is probable that the oxidation of pyruvic acid by the parasite follows a mechanism similar to the tricarboxylic acid cycle of carbohydrate oxidation in mammalian muscle.

The effect of atabrine and quinine on the enzymes of the systems discussed above has been studied. 0.001 M quinine inhibits the over-all process of lactate formation from glucose as well as the enzymes hexokinase and lactic dehydrogenase. However, it seems improbable that sufficient concentrations of quinine to cause these effects are ever obtained *in vivo*. With "physiological" concentrations of quinine, the principal effect seems to be upon pyruvate oxidation. [Work done under contract with the Office of Scientific Research and Development.]

**Effect of methylxanthines on the hypocoagulability produced by chloroform liver damage in**

dogs. JOHN B. FIELD (by invitation), L. GRAF (by invitation), A. SVEINBJORNSSON (by invitation) and KARL PAUL LINK. *Dept. of Biochemistry, Univ. of Wisconsin, Madison.* In previous studies it was indicated that the oral administration of methylxanthines (caffeine, theobromine and theophylline) induces in various species elevated levels of plasma prothrombin (*J. Biol. Chem.* 156: 725, 1944) and fibrinogen (*J. Biol. Chem.*, in preparation). The hepatotoxic action of chloroform is known to result in a hypocoagulability of the blood due to a prothrombin and fibrinogen deficiency.

Measured quantities of chloroform were given to dogs by means of a stomach tube. In repeated trials with the same dogs, this technique gave a reproducible reduction in the prothrombin and fibrinogen levels. When caffeine, theobromine, theophylline and adenine were given orally, two days prior to the administration of chloroform, with the chloroform, and two days after the chloroform feeding, a reduction from the pre-test prothrombin and fibrinogen level did not occur. The following compounds provided a partial protection against the chloroform induced hypocoagulable manifestations: creatine, creatinine, guanidine, and uracil. Little or no protection was afforded by xanthine, guanine, uric acid, arginine, allantoin, urea and vitamin K.

Following the test administration of chloroform, icterus was frequently observed in the plasma, and the capacity of the liver to remove the bromsulphalein test dye from the blood stream was considerably reduced. These indications of hepatic dysfunction were not prevented by the supplementary feeding of methylxanthines even when the methylxanthines prevented a hypoprothrombinemia or depression in the plasma level of fibrinogen.

**Hypercoagulability and hepatic dysfunction induced by compounds of mercury, arsenic, antimony and bismuth.** JOHN A. FIELD (by invitation), EARL G. LARSEN (by invitation) and KARL PAUL LINK. *Dept. of Biochemistry Univ. of Wisconsin, Madison.* Intramuscular injection of organic or inorganic compounds of mercury, arsenic, antimony or bismuth readily induced increased levels of plasma prothrombin and fibrinogen in dogs and rabbits. The extent of the response, and its duration, was proportional to the dose given. When the test compound was administered orally or intravenously less uniform results were obtained.

An exhaustive study was made of the effects produced by the mercurial drug, salyrgan. The hypercoagulability induced by salyrgan could not be attributed to hemoconcentration resulting from diuresis. When the drug was injected daily over a 7-day test period, hyperprothrombinemia and increased plasma fibrinogen levels were maintained. In dogs, salyrgan counteracted the hypoprothrom-

binemic effects of the anticoagulant, 3,3'methylenebis(4-hydroxycoumarin).

The intramuscular administration of a small dose (0.1-1 mg. per kg.) of antimony and potassium tartrate produced a state of hypocoagulability. Somewhat larger doses (1-10 mg. per kg.) gave a transitory period of detectable liver damage and hypoprothrombinemia, followed by a prolonged period during which plasma prothrombin and fibrinogen were markedly increased above normal. Large doses (15-30 mg. per kg.) of the drug gave evidence of frank liver damage; failure to retain the bromsulphalein test dye, icterus, hypoprothrombinemia, fibrinogen deficiency, and finally death.

It is not entirely possible to attribute the experimental changes to a specific hepatocentric effect following the intramuscular administration of the drugs tested. The possibility of tissue damage interfering in those tests wherein the drug was administered by the oral and intravenous routes cannot be discounted. In some tests, where no tissue damage could be discerned, characteristic hypercoagulable changes were obtained.

**Liver lecithin as related to the choline and fat content of the diet.** WILLIAM H. FISHMAN (by invitation) and CAMILLO ARTOM. *Dept. of Biochemistry, Bowman Gray School of Medicine, Winston-Salem.* Two to three months old rats were maintained for 19 days on experimental diets containing casein 10 per cent, minerals 4, cod liver oil 5, ruffex 2, B vitamins, and variable amounts of "Crisco" (5 to 35 per cent) and carbohydrates (sucrose, dextrin 1:1) (74 to 44 per cent). In the liver of all these animals the neutral fats increased and the lecithin level was below normal.

When the diets were supplemented, after seven days, with choline, the fatty infiltration was reversed in every case, as expected. In animals on low fat diets, the lecithin level was only slightly affected by choline supplementation: this is in agreement with our previous results. On the other hand, when the proportion of total fat in the diet was raised above 20 per cent, the effects of choline supplementation on the liver lecithins became marked and values as high as in the livers of normal animals were found.

It seems, therefore, that in the conditions of these experiments, the level of lecithins in the liver is dependent on the dietary supply of both choline and fat. [Aided by a grant from the John and Mary R. Markle Foundation.]

**Phospholipid turnover in plasma and liver of rats studied with P<sup>32</sup>.** EUNICE V. FLOCK and JESSIE L. BOLLMAN. *Division of Experimental Medicine, The Mayo Foundation, Rochester, Minn.* Sodium diphosphate containing P<sup>32</sup> was injected intravenously in rats which had been fasted for 24 hours. Measurements of concentration and radioactivity of the inorganic phosphate and phospho-

lipid of both plasma and liver were made after intervals of time varying from one-half to six hours. Penetration of the labeled inorganic phosphate into the liver occurred very rapidly. The specific activity of the inorganic phosphate of the liver was 75 per cent of that of the plasma after one-half hour, and did not decrease as rapidly as did the specific activity of the plasma so that it was considerably higher than the plasma from the first to the sixth hour.

Incorporation of the labeled inorganic phosphate in the liver phospholipids began promptly and continued to increase during the period studied. From the ratio of the specific activities of these two substances, it can be calculated that the average percentage of newly synthesized phospholipid in the liver after one-half, one, two, four and six hours was 0.3, 1, 6, 30 and 50 respectively.

A small amount of labeled phospholipid was found in the plasma after two hours. After four hours the specific activity of the phospholipid in the plasma was similar to that in the liver, which indicates that a complete replacement of plasma phospholipid by liver phospholipid has then occurred. It is apparent that such replacement would require the release of only a small percentage of the total liver phospholipids since the average concentration of phospholipid P was 3.6 mg. per 100 ml. in plasma, and 136 mg. per 100 g. in liver.

**Serum diastase in rats with alloxan diabetes.**  
 ALFRED H. FREE (by invitation), ELINOR M. ZORN (by invitation) and VICTOR C. MYERS. *Dcpt. of Biochemistry, School of Medicine, Western Reserve Univ., Cleveland.* Blood or serum diastase (amylase) has been studied in human diabetes mellitus during the past 30 years but no unanimity of opinion exists concerning the relationship of changes of the enzyme concentration in this disease. This may in part be explainable because of the various types of diabetes and by the extent of treatment of the patients under consideration. Results of studies in pancreatectomized animals with experimental diabetes are subject to criticism since removal of the pancreas involves removal of acinar tissue (amylase producing) as well as removal of islet tissue (insulin producing).

The present report describes studies of serum diastase (amylase) in adult albino rats with experimental diabetes produced by the intraperitoneal injection of alloxan in amounts of 200 mg. per kg. body weight. Control studies of serum diastase were made along with studies of the enzyme concentration at intervals following the injection of the alloxan. In general there appears to be a temporary increase in serum diastase which is seen approximately 6 hours after the injection of alloxan. Following this the enzyme concentration returns to normal or subnormal concentrations at 48 hours at which time the blood sugar is markedly

elevated. The significance of these results will be discussed.

**Effect of nucleates on methylene blue decolorization by tissue extracts.** JESSE P. GREENSTEIN and HAROLD W. CHALKLEY. *National Cancer Inst., National Inst. of Health, Bethesda.* Aqueous tissue extracts, containing reducing systems, possess the capacity of decolorizing methylene blue under anaerobic conditions. We have observed that when sodium yeast nucleate is added to such extracts the decolorization rate is slightly decreased; when sodium thymus nucleate is added this rate is very considerably decreased. The extent of this decrease in rate is proportional to the amount of nucleate added. Addition of xanthine results in an increase in decolorization rate which appears to be very nearly the same whether nucleate is present or not. The percentage increase in rate or addition of substrate however is greatest in the presence of thymus nucleate. Nearly identical results are obtained with freshly-mixed solutions and with mixtures which are allowed to stand until the viscosity of the thymus nucleate is reduced nearly to that of the extract (enzymatic depolymerization). These and other findings suggest that thymus-type nucleates participate in the regulation of certain oxidation-reduction processes.

**Relationship between calcification of eggshell and carbonic anhydrase activity.** MARIE S. GUTOWSKA and U. C. POZZANI (introduced by Julia O. Holmes). *Massachusetts Agricultural Experiment Station, Amherst.* Previous study in this laboratory has shown a direct relationship between the activity of carbonic anhydrase in the shell gland of the hen and the calcification of the eggshell. The administration of sulfanilamide—a strong inhibitor of this enzyme—resulted in an inhibition of eggshell calcification.

The present report presents a study of the effect of NaCNS, KMnO<sub>4</sub>, and MnSO<sub>4</sub>, on the activity of carbonic anhydrase and on eggshell calcification.

Rhode Island Reds of known laying capacity were used in confined laying batteries.

The possible inhibitors of carbonic anhydrase were administered either subcutaneously or orally. Meldrum and Roughton's manometric method was used for determining carbonic anhydrate activity in the blood and the shell gland, a new unit having been devised for expressing the activity of this enzyme. The quality of the eggshell calcification was determined by the eggshell breaking strength.

The administration of NaCNS was followed by (a) an inhibition in carbonic anhydrase activity of both blood and eggshell gland, and (b) a lowering in quality of the eggshell. These changes were similar to those observed following sulfanilamide administration.

In contrast, KMnO<sub>4</sub>, although a good in-vitro

inhibitor of carbonic anhydrase, had little effect when administered to hens.

The administration of MnSO<sub>4</sub> was followed by an increase in the carbonic anhydrase activity in the hen when administered orally or subcutaneously.

Finally, carbonic anhydrase activity was studied in relation to well-known seasonal variations in breaking strength of the eggshell. A direct relationship was found.

**The effects of lethal doses of various inhibitors of carbohydrate metabolism on the rabbit.** PHILIP HANDLER. *Dept. of Biochemistry, Duke Univ. School of Medicine, Durham.* The subcutaneous administration of fluoride, cyanide, azide and malonate, in doses which were fatal within two to five hours, produced virtually identical effects. Blood glucose and lactic acid and serum inorganic phosphate all increased three to six fold so that the terminal values were: glucose 300-600 mg. per cent, lactic acid 100-250 mg. per cent, and phosphate 10-20 mg. per cent. The behavior of serum organic phosphate was not consistent but it usually increased two or three fold while blood pyruvate increased from 0.5-1.0 mg. per cent to 3.0-5.0 mg. per cent. All these changes were most pronounced during the last 30 minutes of life. The response to iodoacetate differed in that there frequently occurred a marked drop in both inorganic phosphate and lactate during the first 60-120 minutes followed by a sharp rise so that the terminal values were 6-8 mg. per cent of phosphate and 80-140 mg. per cent of lactate. Of this series only malonate induced a  $\beta$ -ketonemia. Large doses of insulin prevented the rise in glucose but not the other changes in blood constituents. Alloxan diabetic rabbits showed an even more dramatic rise in blood sugar under these conditions while the blood glucose of starved animals increased to a lesser extent.

**A convenient ultra-micro titrimetric method for the estimation of amino acids.** ALBERT HIRSCHMAN (by invitation), ALBERT E. SOBEL and LOTTIE BESMAN (by invitation). *Division of Biochemistry, Jewish Hospital of Brooklyn.* By treating the reaction products of ninhydrin and amino acids with hydrogen peroxide, the ammonia can be determined by direct aeration, with no intermediate steps.

One ml. of solution containing 20-100  $\gamma$  of carboxyl nitrogen, 0.3 ml. of buffer solution (10 per cent solution of citrate buffer, of pH 2.5) and 50 mg. of ninhydrin are added to a micro-aeration tube, and heated in a boiling water bath for 10 minutes. The tubes are shaken after 2 minutes heating. Three drops of 30 per cent hydrogen peroxide are added, and the tubes are heated for an additional 3 minutes. The tubes are cooled and set up for aeration as described for Kjeldahl nitrogen (Sobel, Mayer and Gottfried, *J. Biol. Chem.* 156:

355 (1944)). One ml. of saturated potassium hydroxide is added, and the solutions are aerated for 40 minutes. The ammonia is trapped in 1.5 ml. of a 2 per cent boric acid solution containing 2 per cent of an alcoholic mixture of 10 parts of 0.1 per cent bromocresol green and 1 to 2 parts of 0.1 per cent methyl red. The solutions are titrated with 0.0714 N acid, using a capillary microburet. Quantitative results were obtained with most of the 18 amino acids tested. Low results were obtained with cystine (13 per cent) cysteine (75 per cent) tryptophane (50 per cent) and hydroxyproline (29 per cent).

Without the hydrogen peroxide step, or by using a weaker alkali, incomplete recoveries were obtained even with pure ammonium salts.

**Blood changes following administration of protein hydrolysates.** WM. S. HOFFMAN and DONALD D. KOZOLL (by invitation). *Hektoen Inst. for Medical Research, Cook County Hospital, Chicago.* When 45 grams of protein hydrolysate (Parenamine, Stearns or Cutter's amino acids) of 4.5 per cent concentration in solution, were injected intravenously into hospital control subjects at a rate of 300 cc. an hour the amino acids were promptly removed from the circulation. The plasma amino acid nitrogen level rose from a base level of 3-8 to 8-11 mg. per 100 cc. about midway through the injection, returning to normal within one to two hours after the injection. Similar curves were obtained with oral or subcutaneous administration, except that the return to normal was slower.

Serum inorganic phosphate levels dropped significantly early during the injection, returning to normal within an hour after the injection. When glucose was injected just before amino acids, the drop in phosphate due to glucose injection was further depressed by amino acid injection. Blood urea N rose toward the end of the period or after the injection. When the rise was significant, there was usually a diminished urea clearance, so that the rise appeared to be associated with diminished excretion. Blood glucose tended to rise toward the end of the injection period.

The phosphate drop, occurring much earlier than the rise in urea, may not be due to phosphorylation of the deaminized moiety, but to some process that is concerned with the immediate utilization of amino acids by the cells. This might account for the remarkable speed with which amino acids are removed from the circulation.

**A simple method for the determination of N'-methylnicotinamide in urine.** JESSE W. HUFF (by invitation), W. A. PERLZWEIG and MARY W. TILDEN (by invitation). *Dept. of Biochemistry, Duke Univ. School of Medicine, Durham.* N'-methylnicotinamide reacts with acetone in aqueous alkaline solution to produce a green fluorescent substance; excess of acid changes this into another

more stable blue fluorescent compound. Najjar et al. (*Bull. Johns Hopkins Hosp.* 74: 373 1944) observed independently that the fluorescent derivative, F<sub>2</sub>, reacts with acetone and alkali to produce a colored compound which fluoresces on extraction into butanol.

Procedure: to 1.00 ml. of urine diluted to contain 0.3-1.5 γ of N'-methylnicotinamide, in fluorometer tubes graduated at 10 ml., are added 0.5 ml. of acetone (redistilled over KMnO<sub>4</sub>) and 0.20 ml of 6 N NaOH with mixing. After standing at room temp. for 5 minutes 0.30 ml. of 6 N HCl are added, the mixture is heated in a boiling water bath for 2 minutes, cooled, 1 ml. of 20 per cent solution of KH<sub>2</sub>PO<sub>4</sub> is added and the contents are diluted to 10.00 ml. A blank solution is prepared as above simultaneously, but substituting 0.5 ml. of water for the acetone. For the standard a recovery tube is prepared from the same urine diluted in such a way that 1 ml. contains 0.4-0.6 γ of added N'-methylnicotinamide and treated as above. The fluorescence, which is stable for days, is read in any fluorometer equipped with the filters used for the determination of thiochrome. Highly pigmented urines low in N'-methylnicotinamide and those giving high blank values may be first decolorized with charcoal in 2 per cent acetic acid solution. (This work was done in part under a contract with the Office of Scientific Research and Development; it was also aided by the Nutrition Foundation, the John and Mary R. Markle Foundation and the Duke Univ. Research Council).

**Specificity of polygalacturonase.** EUGENE F. JANSEN and L. R. MACDONNELL (introduced by Hans Lineweaver). *Western Regional Research Laby., U.S.D.A., Albany, Cal.* The action of polygalacturonase, an enzyme of the pectinase complex responsible for glycosidic hydrolysis of pectin, must be preceded by de-esterification. This requirement was shown by measurement of the initial rates, the course, and the extent of the action of polygalacturonase (freed of pectinesterase by acid treatment) on pectin and on pectinic and pectic acids prepared with alkali and orange pectin-esterase. The initial rates on all pectinic acids were identical; however, the greater the methoxyl content the sooner the rate departed from the initial linear rate. With pectic acid the hydrolysis by polygalacturonase occurred in two stages, an initial rapid stage up to about 50 per cent hydrolysis of the glycosidic bonds, followed by a slow stage. From a study of the kinetics the second stage appears to be the hydrolysis of digalacturonide. The extent of hydrolysis was a function of the degree of de-esterification. For a given methoxyl content the extent was greater for the enzyme-than for the alkali-prepared pectin acid. The measurable rate of hydrolysis of pectin was only  $\frac{1}{15}$ th of that of pectic acid. It seems reasonable to assume

that the glycosidolysis of pectin occurred because isolated pectins are only about two-thirds esterified; fully esterified pectin might not be hydrolyzable by polygalacturonase.

Fifty per cent of the total viscosity change had occurred when 2 per cent of the glycosidic bonds of the substrates were hydrolyzed. Heat, which causes a decrease in viscosity of pectin, was shown to produce a similar glycosidic hydrolysis of pectin at pH 3.5.

On the formation of acetylcholine by choline acetylase. H. M. JOHN and D. NACHMANSON (introduced by H. T. Clarke). *Dept. of Neurology, Columbia Univ., New York.* According to a new concept the release of acetylcholine (ACh) is a primary event responsible for the alterations of the nerve membrane during the passage of the impulse. Since the chemical energy released by the breakdown of phosphocreatine is adequate to account for the electric energy released by the nerve action potential it was concluded that energy-rich phosphate bonds are used for the synthesis of ACh. In accordance with this assumption an enzyme, choline acetylase, has been extracted from brain which in the presence of adenosinetriphosphate forms ACh in cell-free solution.

In fresh brain extracts in which 100-150 μg of ACh are formed per hour per grain of tissue, fluoride and eserine are necessary to inhibit the action of adenosinetriphosphatase and choline esterase. In extracts prepared from acetone dried brain addition of fluoride is unnecessary since the adenosinetriphosphatase appears to be removed. Addition of eserine has little or no effect since most of the choline esterase is destroyed by acetone precipitation.

On dialysis, the enzyme loses its activity. 1 (+) glutamic acid and cysteine (still more strongly) reactivate the enzyme. The presence of potassium is necessary, for both the dialyzed and undialyzed enzyme, in concentration close to that found in brain. α-Keto acids inhibit the enzyme in concentrations of  $10^{-3}$  to  $10^{-4}$  M, which are close to those occurring in the living cell. Benzoylacrylic acid was found to inhibit the enzyme in  $10^{-5}$  M concentration. Progress is underway to accomplish purification of the enzyme.

**Physico-chemical and biological properties of oxidized cellulose.** ELVIN A. KABAT, G. GEORGE HENNIG (by invitation) and JOSEPH VICTOR (by invitation). *Dept. of Neurology and Medicine, Columbia Univ., Neurological Inst. and Goldwater Memorial Hospital, New York.* The introduction for surgical use of a "soluble cotton" prepared by oxidation with nitrogen tetroxide makes a study of its properties desirable. Two preparations were available, CS1 and CS2, containing 16 and 21 per cent carboxyl respectively. Both were readily soluble in sodium bicarbonate or carbonate solu-

tions. 1 per cent solutions of CS1 showed an osmotic pressure of 155 mm. of water. Molecules of CS2 passed through the membrane and constant pressures were not obtained. Two boundaries were obtained on electrophoresis at pH 7.4 in 0.15M NaCl  $\pm$  0.02M phosphate, a smaller immobile one and a main component with a mobility of about  $-11 \times 10^{-5}$  cm<sup>2</sup>/volt-sec. for CS1 and  $-13 \times 10^{-5}$  cm<sup>2</sup>/volt-sec. for CS2. Rabbits tolerated intravenous injections totalling 3.4 to 7.3 grams during 2 to 5 days. Rises in rectal temperature from 0.4 to 2.5°C. followed single injections of from 0.5 to 2.4 gm. Erythrocyte sedimentation rate was unaffected. Microscopic examination of all tissues 1 to 2 days after injection revealed that the only noteworthy change was a marked swelling of some of the renal convoluted tubules without evidence of necrosis. The fate of these substances in the body was followed immunochemically by taking advantage of their reactivity with Types III and VIII antipneumococcus horse serum. Precipitin tests showed that about 80 per cent of the injected material disappeared from the blood stream in 24 hours and that large amounts appeared in the urine within 3 hours after injection. CS1 was not anaphylactogenic in guinea pigs. [Aided by grants from the William J. Matheson Commission and the Commonwealth Fund.]

Spectrophotometric analysis of purine compounds and their enzymes in the ultraviolet. H. M. KALCKAR. Division of Nutrition and Physiology, Public Health Research Inst. of The City of New York. A combination of optical and enzymatic micro methods has been developed which permits determination of fractions of a microgram of hypoxanthine, guanine, inosine, adenosine and muscle adenyllic acid. The enzymes involved in oxidation and deamination of the purines and of the nucleosides as well as the nucleosidases have also been studied by these methods. The methods and some of the more important applications will be described.

Simplified tests for thiamine in rice. M. C. KIK (introduced by Barnett Sure). College of Agriculture, Univ. of Arkansas, Fayetteville. Short procedures for thiamine analysis were tried on samples of rough, brown, undermilled and milled rice as follows:

One: The regular thiochrome method.

Two: The same as one, without takadiastase; values ranged lower, from 15.4 per cent for milled rice to 19.7 per cent for brown and unpolished rice.

Three: Cold 25 per cent KCl—2 per cent acetic acid extraction. The thiamine content of rough rice was practically the same as with the regular method; brown rice showed 11.7 per cent difference. Unpolished rice was the same as in one; milled rice showed a 10 per cent decrease.

Four: Hot 25 per cent KCl—2 per cent acetic

acid extraction. Rough rice showed a 17.5 per cent decrease; brown rice and unpolished rice had similar values as in three; milled rice showed the same as in one.

Five: Extraction and enzyme hydrolysis took place as in one. Purification with decalco was eliminated, and instead, clear extracts obtained after incubation were immediately treated with isobutyl alcohol and oxidized (adequate portions) as in one. Differences ranged from 30.0 per cent in unpolished to 55.3 per cent in rough rice. [Aided by a grant from the Williams-Waterman Fund of the Research Corporation.]

Phosphorylation of glucose induced by oxidation of l(+) -glutamate by brain in vitro. J. RAYMOND KLEIN. Dept. of Psychiatry, Univ. of Illinois College of Medicine, Chicago. Homogenates of cat brain in potassium phosphate buffer pH 7.0, containing nicotinamide, diphosphopyridine nucleotide, fluoride, and arsenite, oxidized l(+) -glutamate to  $\alpha$ -ketoglutarate. In the presence of glucose, the oxidation was accompanied by conversion of inorganic to organic phosphate, the major portion of which was identified as a mixture of phosphoglycerate and fructose phosphates. The oxygen uptake was greater than the sum of that required for formation of ketoglutarate, estimate: from ammonia production, and that used in the presence of glucose alone. The formation of phosphoglycerate and the extra oxygen uptake may be accounted for in part by assuming dismutation between  $\alpha$ -ketoglutarate and triose phosphate, and oxidation of the expected product,  $\alpha$ -hydroxyglutarate, to ketoglutarate. Hydroxyglutarate was oxidized by the tissue preparation, and, in the presence of glucose, phosphoglycerate was formed. Since carbon dioxide was not formed during the oxidation of glutamate in the presence of glucose, the formation of fructose phosphates cannot be attributed to oxidation of ketoglutarate or four-carbon dicarboxylic acids. It appears, therefore, that oxidation of l(+) -glutamate to  $\alpha$ -ketoglutarate and ammonia may be coupled with phosphorylation of glucose.

Enzymatic oxidation of uric acid. FRIEDRICH KLEMPERER. Massachusetts General Hospital and Dept. of Medicine, Harvard Medical School, Boston. During oxidation of uric acid with uricase prepared from beef kidney or pig liver, only a small fraction of one equivalent of CO<sub>2</sub> was formed. This indicates that in addition to allantoin, which can be isolated from the mixture, substances which contain all 5 carbon atoms of uric acid were formed. When oxidation was carried out in borate buffer of pH 9.2 a substance was formed which contained 4 nitrogen atoms, all of which were liberated by nitrous acid. The only oxidation product of uric acid with these properties is urostanic acid. When the oxidation was performed in phosphate buffer of pH 7.2, the reaction mixture contained allantoin

and a compound which contained 5 carbon atoms and 4 nitrogen atoms, only two of which reacted with nitrous acid. The only known oxidation product of this description is hydroxycetylene-diureine-carboxylic acid. At hydrogen ion concentrations intermediary to those mentioned above, the amount of nitrogen liberated from substances other than allantoin by nitrous acid varied between 2 and 4 equivalents indicating that in addition to allantoin varying amounts of uroxanic acid and hydroxy-acetylene-diureine-carboxylic acid were formed. The relative quantity of each substance formed depended on the concentration of hydrogen ions as well as buffer ions. All three substances were stable in the presence of urease. It is concluded that the primary oxidation product of uric acid is an extremely unstable compound which decomposes immediately into the three compounds identified in the reaction mixture. The latter decomposition, in all probability, is not enzymatic.

**Errors in the estimation of the free fatty acid content of dried eggs.** LEO KLINE and C. M. JOHNSON (introduced by Hans Lineweaver). *Western Regional Research Lab., U. S. D. A., Albany, Cal.* A current study of lipolytic activity in stored dried egg powders necessitated the use of a specific method for the measurement of glyceride hydrolysis. The A.O.A.C. method for the acidity of ether extracts of dried eggs has been generally used for this purpose. Indiscriminate use of results thus obtained may be misleading for two reasons: (1) Fatty acids liberated during storage may be underestimated, as shown by the following results. Mixtures of oleic acid and whole fresh egg were frozen and vacuum dried. The recovery of the oleic acid was only about 55 per cent when the extraction was made at the normal pH (8.5-9.0) of freshly dried egg. (The pH was measured on emulsions consisting of 1 part of egg to 3 parts of distilled water.) It was necessary to adjust the egg mixture to a pH of 4 to 5 before drying, to obtain 95 to 100 per cent recovery of the added oleic acid. (2) Approximately 70 per cent of the acidity of the ether extract of several freshly dried egg samples was found to be due to non-free fatty acid material (phospholipid), precipitable by acetone. Egg cephalin, unlike lecithin, behaves as a monobasic acid when titrated in solvents of low dielectric constant, and is believed to be largely responsible for the acidic nature of the acetone-insoluble fraction of egg oil. Failure to correct for these two factors may mask significant increases in free fatty acids during storage of dried egg.

- Intravenous injection of vitamin D. ALFRED E. KOEHLER and FLORENCE CONNOLLY (by invitation). *Santa Barbara Cottage Hospital and Sansum Clinic, Santa Barbara, Cal.* Crystalline vitamin D (Winthrop) equivalent to 160,000 U.S.P. units was dissolved in 4 cc. propylene glycol and a colloidal

suspension was made by the addition of 200 cc. normal saline. This amount was then injected intravenously at constant rate over a 2 hour period into 11 young adults. Blood was taken for serum calcium and phosphorus at the end and at various times after the period of injection.

The serum calcium response was varied and unpredictable. In 11 subjects the maximum elevation of calcium was 4.4 mg. per cent, the minimum -1.8 per cent, and the average +1.7 per cent. The maximum change occurred as soon as "at the end of the injection" or as late as "5 days after."

The serum phosphorus generally decreased slightly but in a few instances there was an elevation.

To obtain an approximate idea of the amount of calcium mobilized to bring about the serum level changes after vitamin D injection, various concentrates of calcium lactate were injected at a constant rate in a similar manner as with vitamin D, over a 2 hour period. One gm. of calcium, as the lactate, produced a serum rise at the end of injection approximately equivalent to the maximum effect of vitamin D at the same time interval. It seems improbable that this amount could represent increased absorption from the alimentary tract in two hours; hence these experiments indicate that the calcium must be mobilized at least in part from the bone.

The variable response to vitamin D under standard conditions indicates that other systemic factors must operate to condition the response.

**Intravenous testosterone tolerance.** ALFRED E. KOEHLER and ELSIE HILL (by invitation). *Santa Barbara Cottage Hospital and The Sansum Clinic, Santa Barbara, Cal.* A colloidal solution of testosterone prepared by dissolving the sterol in a small quantity of propylene glycol and adding a larger amount of normal saline is not sufficiently stable for prolonged intravenous injection. We have overcome this difficulty by dissolving 100 mg. of testosterone in 20 cc. of propylene glycol and injecting this by means of an electrically driven constant rate pump simultaneously with 200 cc. of normal saline by means of another pump. A T tube connects the two pumps to a Kaufman-Luer syringe which acts as a mixing chamber for the production of the colloidal solution. Both pumps are timed to deliver their contents in 2 hours.

Injections were given 6 subjects, 4 males and 2 females without endocrine disturbances.

For the 5 hour period following the start of the injection, the extra urinary androgen excretion increased about 10 fold for the hourly rate over the control period and 14.3 per cent of the injected testosterone was excreted. All the extra androgen was excreted in the first 24 hours following the injection. The extra androgen received ranged from 15 to 31.6 per cent (average 23.4) of the injected

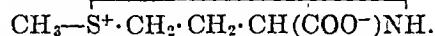
testosterone. The extra excretion in the female subjects fell within the limits of the values for the males. On the second and third day after the injection the androgen excretion was depressed below that of the average of the 4 to 5 day control period before the injection. The injected testosterone probably depresses testicular secretion.

**Quinine absorption during avitaminosis.** GRANVIL C. KYKER and MILDRED McEWEN (introduced by James C. Andrews). *Dept. of Biological Chemistry and Nutrition, School of Medicine, Univ. of North Carolina, Chapel Hill.* The postulation of a mutual metabolic inter-relationship between quinine and members of the vitamin B complex has been the basis for experiments which have been reported herein for the past two years. This report concerns the effect of an acute deficiency of vitamin B complex on the rate of the intestinal absorption of quinine. Comparable doses of quinine were administered by a special stomach tube technique to each of thirty-six normal rats and to an equal number which were in an acute stage of deficiency. Six animals from each series were sacrificed at 15, 30, 45, 60, 120, and 180 minutes after administration of the alkaloid. The unabsorbed portion was determined by a modified Cori method. Each alimentary tract was divided into gastric and intestinal portions which were analyzed separately. No difference was observed in the rates of absorption exhibited by the two series of animals. In both the normal and deficient animals the rate of absorption decreased with time. The passage of the dose from the stomach to the intestine was more rapid in the deficient animals, without exception. This difference in rate of evacuation was pronounced at first and continued significantly at three hours. Each of the conclusions is in contradiction to the effect of similar vitamin deficiencies on the motility and absorption of food substances. These unexplained differences evidently reside in the pharmacological action of the drug.

Roentgenographic confirmation of our observations, after incorporation of quinine in a barium meal, is in preparation. [Supported by a grant from the Samuel S. Fels Fund.]

**Dehydromethionine, a new methionine derivative.** THEODORE F. LAVINE. *Lankenau Hospital Research Inst., Philadelphia.* In a previous report (J. Biol. Chem. 151: 281, 1943) of the reversible reaction of methionine with I<sub>2</sub>, the reaction product, which was not isolated, was, for convenience, referred to as methionine periodide although some of its properties were at variance with this conception. It has since been found that the product is iodine-free and differs from methionine only by the loss of 2 H-atoms and accordingly the name, dehydromethionine, is proposed for the compound. Its formation is represented by the equation, C<sub>5</sub>H<sub>11</sub>SNO<sub>2</sub> + I<sub>2</sub> → C<sub>5</sub>H<sub>9</sub>SNO<sub>2</sub> + 2 HI; which is

confirmed by quantitative evidence of acid and iodide formation, and by analysis of the isolated compound. The structure assigned to this compound is that of tefrahydro-1-methyl-2μ1-azathio-lium-3-carboxylate,



A crystalline product was obtained by adding ether to a methyl alcohol solution of crude dehydromethionine; the latter was formed by evaporation of the supernatant liquid resulting from reaction of the calculated amount of methyl alcohol I<sub>2</sub> with methionine in the presence of a slight excess of silver oxide. Analysis; calculated for C<sub>5</sub>H<sub>11</sub>SNO<sub>2</sub>: C, 40.81; H, 6.17; N, 9.52; S, 21.79; found C, 40.03; H, 6.45; N, 9.72; S, 21.26 (averages of two determinations). The isolated material is extremely hygroscopic which is perhaps reflected in the above values.

Methionine sulfoxide is formed in aqueous solutions, very slowly at pH 7 (phosphate exerts a specific accelerating effect), rapidly in acid or alkaline solution.

The ease of formation of dehydromethionine and its stability at pH 7 suggest biological importance.

**Isolation of two transaminating enzymes.** L. F. LELOIR (by invitation) and D. E. GREEN. *Dept. of Medicine, College of Physicians and Surgeons, Columbia Univ., New York.* Braunstein and Kitzmann described transamination, a process in which amino groups are transferred reversibly from amino acids to keto acids. Considerable uncertainty has existed as to the number and specificity of the enzymes involved. Braunstein has postulated two enzymes, one specific for glutamate, the other for aspartate. Each enzyme was assumed to catalyze transamination between the primary dicarboxylic acid substrate and various keto acids. Cohen has found evidence of only a single transaminating enzyme in animal tissues, and he has been unable to confirm that amino acids other than glutamate, aspartate and alanine are concerned in transaminations. We have isolated from pig heart two distinct transaminating enzymes: (1) the glutamic-aspartic enzyme which catalyzes the reversible transamination between α-ketoglutarate and aspartate or cysteic acid, and (2) the glutamic-alanine enzyme which catalyzes the reversible transamination between glutamate and pyruvate. No other amino acid or keto acid with the possible exception of mesoxalic acid was activated by either of these two enzymes. The glutamic-aspartic enzyme was isolated homogenous as judged by the usual criteria (QTN 47,500). The glutamic-alanine enzyme was obtained about 40 per cent pure by salt fractionation, and the active component could be separated from the mixture by electrophoresis (QTN 222,000). Glutamic-aspartic and glutamic-alanine enzymes account respectively for about 3 per cent and 0.1

per cent of the dry weight of pig heart. No evidence was found of dissociable prosthetic groups or of significant amounts of B complex vitamins in either enzyme.

**Kinetics of enzymes producing the Streptococcus faecalis R-stimulating factor.** JULIA G. LEMON and JOHN R. TOTTER (introduced by Paul L. Day). *Univ. of Arkansas School of Medicine, Little Rock.* A concentrate of the precursor of *Streptococcus faecalis* R (*S. lactis* R) stimulating factor occurring in yeast extract was made by adsorption on norite, elution, and precipitation with alcohol. This concentrate was used as a substrate for enzymes prepared from rat liver, chicken pancreas, and potato. Initial velocities of the conversion to active *Streptococcus faecalis* R-stimulating substance, at several substrate concentrations, were determined with the three enzyme preparations at pH 7 and 32°. Analysis of the data obtained indicates that under the conditions of the tests the Michaelis constants for the enzyme preparations differ widely. Expressed as the equivalent of mg. of material of potency 40,000 per liter, the *K<sub>m</sub>* for the rat liver preparation is 0.29, for the chicken pancreas enzyme is 3.0, and for the potato enzyme is about 38. [Aided by a grant from the National Live Stock and Meat Board.]

**Effect of low pressure, low temperature, diethyl stilbestrol administration, and starvation on the cholesterol content of serum and of adrenal glands in rats.** LOUIS LEVIN. *Dept. of Anatomy, College of Physicians and Surgeons, Columbia Univ., New York.* Diethyl stilbestrol, known to be an adrenocortical stimulant, causes a rapid and progressive decrease in cholesterol levels of serum and of adrenal glands. The very low cholesterol levels are maintained for as long as the drug is administered (35 days). Despite the adrenal hypertrophy, the cholesterol content of the adrenal glands is far below the normal value.

Subjecting of rats to low barometric pressure causes the adrenal cholesterol level to fall to half the normal value within several hours. There is a rapid restoration to normal levels after return to normal atmospheric pressure. The serum cholesterol is not affected by subjecting to low pressures for the short periods (7 hrs.) used in these experiments.

Exposure to low temperatures (0 to 5° C) for as long as 72 hours has no significant effect on either serum or adrenal cholesterol levels. Likewise, after complete starvation for 72 to 120 hours, the adrenal cholesterol concentration remains normal but the serum cholesterol level is slightly decreased.

In no case, except after hypophysectomy, and in a few cases after treatment with large doses of desoxycorticosterone acetate, were adrenal cholesterol concentrations greater than normal encountered.

These findings, at least in part, support the conclusion of Sayers et al., (Yale J. Biol. and Med. 16: 361, 1944) that severe stresses cause the secretion of adrenotrophic hormone which in turn causes a temporary depletion of adrenal cholesterol, possibly because of accelerated use of this substance in the manufacture of active adrenocortical steroids.

**The catalytic activity of iron compounds in fat autoxidation.** JOHN FLAIG LINGENFELTER and WILFRED A. GORTNER (introduced by L. A. Maynard). *School of Nutrition, Cornell Univ., Ithaca.* The pro oxidant activities of some simple iron salts and cyanide complexes have been studied in storage tests with fresh pork fat in a heterogeneous system, and the extent of autoxidation was estimated by a modified mieroperoxide method.

Certain ferrous salts and complexes have been found to be the most effective catalysts under these conditions. A difference in mechanism is indicated for the catalytic activities of ferrous and ferric iron in catalyzing the autoxidation of unsaturated fats. This supports previous observations that certain octahedral complexes of ferrous iron show marked activity as oxidation catalysts for atmospheric oxidations.

The activity of the compounds tested will be discussed in terms of a general theory of the activity of ferrous iron as an initiator of chain reactions of oxygen. [Aided by a grant from the Consolidated Edison Co. of New York, Inc.]

**The mechanism of sulfanilamide acetylation.** FRITZ LIPMANN. *Biochemical Research Lab., Massachusetts General Hospital, Boston.* Concentrated homogenates of pigeon liver were found aerobically to acetylate sulfonamides vigorously, in particular when acetate was added. Without respiration only negligible acetylation occurred. However the addition of adenylypyrophosphate evoked anaerobically acetylation at a rate comparable to that of the aerobic process. Acetyl phosphate was inactive. It is assumed from these data that respiration merely generates energy rich phosphate bonds to form adenylypyrophosphate, which, on the appropriate enzyme, condenses acetate and sulfanilamide to the acetyl sulfanilamide.

The acetylating system proper, which is thus independent of respiration, may be frozen without loss. By centrifugation of a frozen homogenate, the adenylypyrophosphate-catalyzed acetylation is obtained in a homogeneous, slightly opalescent solution. This solution becomes readily inactive on standing, with or without dialysis. In both cases, the system may be reactivated through addition of boiled extracts of liver or kidney, less effectively of muscle but not of yeast.

**Spectroradiometry of ninhydrin and some derivatives in air-free solutions.** DOUGLAS A. MACFADYEN. *Division of Chemistry and Physics, Army*

*Medical School, Washington.* Ninyhydrin forms many colored derivatives. Some are stable in the presence of air; others are rapidly oxidized by air, and include derivatives of hydrindantin. Elucidation of the mechanism of the chromogenic reactions of ninyhydrin with amino acids, in which hydrindantin has been variously considered,<sup>1,2,3</sup> has been complicated by failure to control pH and oxidation-reduction factors.

Preparation of solutions sufficiently free from air to yield constant spectroradiometric characteristics was difficult in paraffin-sealed cuvettes which were tested in the Beckman quartz prism spectrophotometer; but it was simple in Hamilton-Van Slyke vessels (Fig. 1A<sup>4</sup>) which were used as cuvettes in the Coleman clinical spectrophotometer. These vessels, from which air has been removed by suction, serve for reactions at temperatures up to 100° and also as cuvettes for anaerobic spectroradiometry.

The anaerobic technique was applied to a study of solutions of hydrindantin at varied pH, and to a comparison of the reaction of alpha-alanine with ninyhydrin and the reaction of alpha-alanine with hydrindantin. The results, which could not have been obtained under ordinary spectroradiometric conditions, support none of the previously stated hypotheses.

**Urinary steroids of patients with adrenal diseases.** HAROLD L. MASON. *Dept. of Biochemistry, Mayo Foundation, Rochester, Minn.* Urine was collected from patients with Addison's disease, adrenal hyperplasia and adrenal tumors, hydrolyzed and extracted with ether or benzene. The neutral ketonic alcohols and nonketonic alcohols were separated and chromatographed on aluminum oxide by procedures similar to that of Callow and Callow (Biochem. J. 33: 931). From 126 liters of pooled urine of men with Addison's disease treated with desoxycorticosterone acetate, 96 mg. of androsterone, the only crystalline ketone, and 1 mg. of pregnanediol were isolated. Eighteen liters of urine from a young woman with Addison's disease and normal menstrual cycles gave 28 mg. of neutral ketonic fraction which assayed 7.5 mg. of 17-ketosteroid and gave 8 mg. of alcoholic ketone. In accordance with Brooke and Callow (Quart. J. Med. S, 233) large amounts of dehydroisoandrosterone (isolated as the sodium sulfate in 2 instances) were obtained from five of six patients with tumors. The following were present in greater than normal amounts: Etioholan-3 $\alpha$ -ol-17-one in five cases with tumor and one of the four with hyperplasia; andros-

terone in three cases with tumor and in three with hyperplasia; pregnanediol in all cases with tumor and in two with hyperplasia; 3 $\alpha$ ,17,20-pregnane-triol in one patient with tumor and three patients with hyperplasia. An unidentified alcoholic ketone, m.p. 197-198° (acetate, 238-240°) was present in relatively large amounts in the urine of all patients with hyperplasia and of three with tumors. A nonketonic alcohol, m.p. 206-207°, 3 $\beta$ ,20 $\alpha$ -pregnanediol and a number of small unidentified fractions were obtained.

**Acetate utilization by animal tissues, using isotopic carbon as a tracer.** GRACE MEDES, SIDNEY WEINHOUSE (by invitation) and NORMAN F. FLOYD (by invitation). *Lankenau Hospital Research Inst., Philadelphia.* In continuation of studies of fatty acid metabolism, using C<sup>14</sup> as a tracer, the conversion of acetate to acetoacetate by various tissues was investigated. Rat liver slices readily oxidize acetate with the intermediate formation of acetoacetate. Kidney and heart slices also oxidize acetate without accumulation of ketone bodies; but since these tissues were found to oxidize acetoacetate more rapidly than acetate, ketone body formation was not excluded. To discover whether acetoacetate is an intermediate of acetate oxidation in kidney, a mixture of carboxyl-labeled acetate, and non-isotopic acetoacetate was incubated with kidney slices. The presence and amount of excess C<sup>14</sup> in the  $\beta$  and carboxyl carbons of the recovered acetoacetate indicated that most of the utilized acetate was converted to ketone bodies. The conversion was direct, and did not involve assimilation of metabolic CO<sub>2</sub>, as shown by the fact that a control experiment with non-isotopic acetate and acetoacetate in presence of isotopic bicarbonate resulted in the recovery of non-isotopic acetoacetate.

In a similar experiment with slices of heart muscle, incubation of isotopic acetate and non-isotopic acetoacetate resulted in the recovery of non-isotopic acetoacetate. Other tissues are being investigated and will be reported.

Apparently, two pathways for acetate utilization exist in animal tissues; one proceeding through acetoacetate, occurs in liver and kidney, the other not involving ketone body formation, occurs in heart and perhaps also in kidney and liver.

**The urinary excretion of riboflavin by man as related to diet and physical activity.** OLAF MICELSEN, DORIS DOEDEN (by invitation) and ANCEL KEYS. *Laby. of Physiological Hygiene, Univ. of Minnesota, Minneapolis.* Eight normal young men were maintained in caloric balance for 160 days on a constant 3300 Cal. diet providing 0.9 mg. of riboflavin daily. Urinary riboflavin stabilized after 6 weeks and averaged 0.120 mg. daily in 4 men who received no supplements and 0.490 mg. in 4 men who received daily supplements of 1.0 mg. of riboflavin.

Twelve similar subjects receiving 2.1 mg. daily

<sup>1</sup> Ruhemann, S. J. Chem. Soc. 99: 797, 1911.

<sup>2</sup> Harding, V. J. and R. M. MacLean. J. Biol. Chem. 25: 345, 1916.

<sup>3</sup> Rettinger, J. M. J. Am. Chem. Soc. 39: 1059, 1917.

<sup>4</sup> Hamilton, P. B. and D. D. Van Slyke. J. Biol. Chem. 150: 231, 1943.

for 4 months excreted an average of 0.670 mg. Complete starvation and hard physical work produced excretions of 1.30, 1.89, and 1.50 mg. on successive days. Acute thiaminosis produced by thiamine deprivation was associated with an average daily excretion of 2.69 mg. of riboflavin although riboflavin intake was unchanged.

Six similar subjects were subjected to 3 periods of bed-rest. Prior to bed-rest they excreted 0.64 mg. of riboflavin daily but this rose in bed-rest to 1.07 mg. and fell abruptly to 0.56 mg. on quitting bed-rest. Riboflavin intakes during the periods corresponding to these excretions were 2.25, 1.62 and 1.93 mg., respectively. Body weight was substantially constant throughout and nitrogen balance was not correlated with apparent riboflavin balance. A simple herniorrhaphy with 3 weeks bed-rest produced similar but greater effects. [This work was supported in part under the terms of a contract between the Regents of the Univ. of Minnesota and the Office of Scientific Research and Development. Support from other sources will be acknowledged in final publication.]

**The effect of bed rest on mineral and nitrogen balances.** ERMA V. MILLER (by invitation), OLAF MICELSEN, W. W. BENTON (by invitation) and ANCEL KEYS. *Lob. of Physiological Hygiene, Univ. of Minnesota, Minneapolis.* Six normal young men were subjected to three and four week periods of bed rest in 10 experiments. Controls for balance studies were run before and after the bed rest. Throughout the experiments, food, urine and stools were collected and analyzed for nitrogen, potassium, phosphorus and calcium.

Body weight remained constant during each entire experiment. Before bed rest, the daily protein intake was 75 grams, whereas it was 55 grams during bed rest. While in bed, the men showed an average negative balance of 11 grams per day. During two bed rest experiments, the protein intake for five days was increased to 130 grams per day. This reversed the negative balance and produced a positive protein balance averaging from eleven to seventeen grams daily. As soon as the protein intake was again reduced, the marked negative balance\* appeared. During the recovery period, the nitrogen balance became positive as soon as the subject got out of bed. It required about two to three weeks to restore the protein lost during bed rest.

The potassium balance was negative during bed rest (169-363 mg. per day). The most negative potassium balances were associated with the highest nitrogen loss but there was no constant relation between them. It required two to three weeks after the bed rest to restore the potassium loss.

The calcium and phosphorus balances were variable during the periods of bed rest. [This work was supported in part under the terms of a contract be-

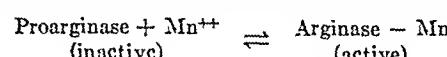
tween the Regents of the Univ. of Minnesota and the Office of Scientific Research and Development. Support from other sources will be acknowledged in final publication.]

Further purification of the enzyme from chicken pancreas which produces the *Streptococcus faecalis* R-stimulating factor. VIRGINIA MIMS (by invitation) and MICHAEL LASKOWSKI. *School of Medicine, Univ. of Arkansas, Little Rock.* A method has been described for the purification from chicken pancreas of the enzyme which produces the *Streptococcus faecalis* R-(*S. lactis* R) stimulating factor from inactive precursors in yeast (Laskowski, Mims, and Day, *J. Biol. Chem.*, in press). Preparation of enzyme made by this method had an average potency of 200 units per mg. of protein, with an average yield of 3000 units per kilo of pancreas. A similar enzyme has been provisionally termed "vitamin B<sub>E</sub> conjugase" (Bird et al., *J. Biol. Chem.* 157: 413, 1945).

Several improvements in the purification procedure have been introduced. By using pH 8 phosphate buffer instead of pH 7 and by permitting the minced pancreas to autolyze for 24 hours at room temperature, one to two million units have been extracted from one kilo of tissue. The purification with calcium phosphate gel and precipitation with alcohol have been retained. The laborious reduction in volume by salting out with sodium sulfate has been abandoned; instead, saturated ammonium sulfate adjusted to pH 7.6 is used for the final fractionation. The purest preparation so far obtained has had a potency of 2000 units per mg. of protein. Concentrated preparations are yellowish, showing a maximum absorption at about 360 m $\mu$ . As yet no definite statement can be made as to whether or not the color is associated with enzymic activity.

**Liver arginase.** MOSTAFA S. MOHAMED (by invitation) and DAVID M. GREENBERG. *Division of Biochemistry, Univ. of California Medical School, Berkeley.* Liver arginase of high potency was prepared by a procedure which involves the preferential denaturation and precipitation of non-arginase proteins by lead ions and acetone. Electrophoretic examination of the best preparations showed the presence of three proteins. The isoelectric point, determined from the electrophoretic mobility and by acetone titration, was in the neighborhood of pH 5.0.

The activation of arginase by Mn<sup>++</sup> and Co<sup>++</sup> was found to be a reversible reaction, concerned with the enzyme alone, and governed by time, temperature, pH, and the type and concentration of the activating ion. The activation seems best explained by the following scheme, using Mn<sup>++</sup> as an example:



The arginase-metallic ion compound is readily dissociated.

Arginase is quite stable in solution and in the presence of most heavy metals; only  $\text{Ag}^+$  and  $\text{Hg}^{2+}$  inactivate it. The enzyme is destroyed by iodine, but not by  $\text{H}_2\text{O}_2$ . The activity is lowered by borate and citrate buffers; probably by the formation of complexes with the activating ions.

Kinetic analysis of the substrate concentration-activity curves and the pH-activity curves yielded the conclusion that the active enzyme-substrate intermediate is formed by combination of one monovalent cation of arginine with one of arginase in the anionic state. The Michaelis-Menten dissociation constant varies with pH to give a U-shaped curve, the minimum value being at about pH 8.0.

**Dietary protein and porphyrin metabolism in the rat.** JAMES M. ORTEN and JUDITH MACKEY KELLER (by invitation). *Dept. of Physiological Chemistry, Wayne Univ. College of Medicine, Detroit.* A study was made to determine the effect of a synthetic diet low in protein (3.5 per cent casein) but adequate in all other respects on the fecal excretion of protoporphyrin in the rat. Control rats were fed the same diet but with the level of casein increased to 22.5 per cent.

The porphyrin content of the feces was quantitatively determined by a modification of Watson's method for protoporphyrin in erythrocytes. Hemoglobin determinations were made by an acid-hematin method at regular intervals during the 16-week period of observation.

The porphyrin excretion of the low-protein rats was consistently less than that of the control animals when calculated either as micrograms of protoporphyrin per day or per 100 grams of body weight, but the excretion was somewhat greater when expressed as micrograms per gram of dietary protein ingested. The porphyrin excretion of the low-protein rats decreased progressively during the experiment while the usual chronic anemia developed.

If protoporphyrin excretion is an index of porphyrin synthesis, these data indicate that dietary protein serves as a precursor of the porphyrin nucleus in the rat and that porphyrin formation, like hemoglobin formation, has a high "priority rating" for available protein in the organism.

**The rôle of dihydrocozymase and inorganic orthophosphate in enzymatic transphosphorylation.** WINSTON H. PRICE (by invitation) and SIDNEY P. COLOWICK. *Dept. of Pharmacology, Washington Univ. School of Medicine, St. Louis.* The following reactions have been studied in fluoride-poisoned aqueous extracts of minced rat muscle:

- (1) Adenosinetriphosphate + glucose  $\rightarrow$  glucose-6-phosphate + adenosinediphosphate
- (2) Adenosinetriphosphate + fructose-6-phosphate  $\rightarrow$  fructose-1,6-diphosphate + adenosinediphosphate

The enzymes catalyzing these reactions are stable at 25° in the pH range 7.0 to 8.0, but are rapidly inactivated at pH 6.0. Extracts which have been inactivated at pH 6.0 can be reactivated by the addition of small amounts of dihydrocozymase. This reactivation can be demonstrated in an iodoacetate-poisoned system, in which the addition of the oxidized form of cozymase has no effect.

In aqueous extracts prepared from acetone-dried rat muscle, the enzymes are stable at any pH in the range 6.0 to 8.0; however, they can be inactivated at pH 6.0 by the addition of an extract of fresh muscle.

Extracts of either fresh muscle or acetone-dried muscle can be inactivated at pH 7.5 by dialysis against saline. The dialyzed extracts can be reactivated by the addition of inorganic phosphate and Mg. The addition of dihydrocozymase is unnecessary in this case. When extracts of fresh muscle are inactivated at pH 6.0 and then dialyzed against saline, the addition of dihydrocozymase, inorganic orthophosphate and Mg is necessary for reactivation.

The possibility of the intermediate formation of an inorganic polyphosphate such as pyrophosphate by the reaction of adenosinetriphosphate with inorganic orthophosphate has been considered. Radioactive orthophosphate is being used for further investigation of this possibility.

**Mode of denaturation of serum albumin by sodium dodecyl sulfate.** FRANK W. PUTNAM (by invitation) and HANS NEURATH. *Dept. of Biochemistry, Duke Univ. School of Medicine, Durham.* In continuation of previously described work (J. Am. Chem. Soc. 66: 692, 1944) on the interaction between horse serum albumin (A) and sodium dodecyl sulfate (D), further data on the composition and molecular properties of the resulting complexes have been obtained. Diffusion and viscosity measurements on mixtures of A and D corresponding to the composition of complexes  $\text{AD}_{55}$  and  $\text{AD}_{110}$  yield molecular weights which agree satisfactorily with the calculated values. Viscosity measurements indicate that formation of  $\text{AD}_{55}$  proceeds without appreciable changes in the shape of the albumin molecule whereas the asymmetry of the protein increases in the formation of  $\text{AD}_{110}$ . Upon addition of more detergent further unfolding occurs with the formation of loose, electrophoretically monodisperse complexes of variable composition, up to a D/A ratio of 1 at which free detergent becomes detectable. Partial removal of detergent, by freezing out from solutions of complexes higher than  $\text{AD}_{110}$ , yields  $\text{AD}_{55}$  and regenerated protein.

The data indicate that the first step in the denaturation of serum albumin by detergent consists of stoichiometric binding of the detergent anions by one-half the cationic protein groups, the remaining basic groups differing in steric arrangement, dissociation constant or structural function. Structural

disorder of the protein ensues when the latter groups react, and is accentuated upon saturation of secondary attractive forces by detergent. The present observations afford a model for the mechanism of protein denaturation and for the interaction between proteins and other ionizable biological compounds.

**Prothrombin of newborn pups born of a mother fed dicumarol.** ARMAND J. QUICK. *Dept. of Biochemistry, Marquette Univ. School of Medicine, Milwaukee.* Pups born of a mother fed dicumarol prior to parturition had a hypoprothrombinemia which was much more pronounced than in the mother. In one instance the prothrombin time of the mother was 21 seconds (5 per cent of normal) while that of the pups ranged from 100 to 240 seconds (less than 0.5 per cent of normal). Four of a litter of 7 died of hemorrhage. In 3 pups death resulted from intraperitoneal bleeding. In none was umbilical oozing observed. The three that survived received a water soluble preparation of vitamin K intravenously. In untreated pups of another similar experiment the prothrombin continued to drop for several days, but returned to the adult level in 8 to 10 days.

Pups are relatively more susceptible to dicumarol than older dogs, but they also show a more rapid recovery. When dicumarol was fed to the nursing mother, the pups had a mild but unmistakable decrease in prothrombin indicating that the drug passed into the milk.

These results offer an explanation for the finding that parturient cows fed spoiled sweet clover hay sometimes survive whereas the calf succumbs to hemorrhage. Dicumarol apparently injures or inhibits the mechanism employed for the synthesis of prothrombin more in the fetus than in the mother. The administration of the drug to pregnant women, on the basis of the present findings, can be considered dangerous particularly to the life of the child.

**Metabolism of acetic acid.** D. RITTENBERG and KONRAD BLOCH. *Dept. of Biochemistry, Columbia Univ., New York.* The administration of deuterio acetic acid and a foreign amine results in the excretion of a deuterio acetyl derivative containing a much lower isotope concentration than the acetate fed. The isotope dilution is inversely proportional to the amount of acetate fed per 100 grams of rat but is nearly independent of the amount and nature of the amine (sulfanilamide, para aminobenzoic acid and d- and L- $\gamma$ -phenyl- $\alpha$ -aminobutyric acids). When alanine labeled with deuterium at the  $\beta$ -carbon atom is fed, together with phenylaminobutyric acid, the excreted acetyl derivative contains deuterium. The intermediate is probably deuterio pyruvic acid. When deuterio alanine is fed, together with para-amino-benzoic acid, or sulfanilamide, the excreted acetyl groups contain very little deuterium.

These and other data suggest that the dilution of the deuterio acetate, at least as observed in the cases of para aminobenzoic acid and sulfanilamide, is the result of dilution of the fed acetate with that produced in the organism. Quantitatively the data suggest that in the case of the rat acetic acid is produced at the rate of 1 gram per 100 gram of body weight per day and that the major sources of this acetate are the fats and the ketogenic amino acids. Since the actual concentration of acetic acid in the tissues is very small the organism must have an efficient mechanism for disposing of acetate. Utilization of acetic acid for some synthetic reactions was demonstrated by the isolation of fatty acids, cholesterol, aspartic and glutamic acids containing C<sup>14</sup> after the feeding of acetate labeled with C<sup>14</sup>.

**Specificity of choline esterase in nerve tissue.** M. A. ROTHENBERG and D. NACHMANSON (introduced by H. T. Clarke). *Depts. of Biochemistry and Neurology, Columbia Univ., New York.* The concept that the release of acetylcholine (ACh) is directly connected with the nerve action potential is based essentially on studies of the enzyme choline esterase. In these investigations it has been assumed that the enzyme studied is specific for ACh. By testing the rate of hydrolysis of different substrates a pattern has been established which makes it possible to distinguish between choline esterase and other esterases not specific for ACh.

Evidence has been provided that the esterase present in all nerve tissues is either exclusively or predominantly specific choline esterase. All those nerve tissues were tested which were essential in laying the basis for the new concept: mammalian brain, abdominal chain of lobster, squid fiber and electric organ of fish. The esterase present in striated and heart muscle, both free of nerve fibers and endings is also choline esterase.

Choline esterase extracted from the electric organ of *Electrophorus electricus* has been purified by means of fractional ammonium sulfate precipitation to a degree where one milligram of protein splits three thousand milligrams of ACh per hour. Some features of this purified preparation will be described. The rate of hydrolysis of different substrates shows the same pattern as freshly homogenized electric tissue. This indicates that the enzyme tested in fresh electric tissue is choline esterase and therefore the parallelism established between voltage and enzyme activity becomes particularly pertinent.

An active solution of choline esterase has now been obtained from the nucleus caudatus of ox, the first choline esterase preparation obtained from mammalian nerve tissue.

**The effect of riboflavin analogues on the growth of *Lactobacillus casei*.** HERBERT P. SARETT (introduced by J. Raymond Klein). *Dept. of Chemistry, Oregon State College, Corvallis.* Isoriboflavin, lumiflavin, and 1-ribitylamino-2-amino-4,5-dimethyl-

benzene were tested for their effects on the utilization of riboflavin for growth of *Lactobacillus casei*. Two types of media, differing in sources of nitrogen and vitamins, were used for growth experiments. One contained hydrolyzed casein and known vitamins, the other alkali-treated peptone and riboflavin-free yeast. Growth was measured by acid titration.

With no riboflavin added to the basal casein medium, isoriboflavin (1-300 $\gamma$  per 10 ml.) has about 0.03 per cent of the activity of riboflavin, in contrast to the antiriboflavin effect of this compound in rats. In the presence of suboptimal levels of riboflavin, isoriboflavin is markedly stimulatory to *L. casei*. The stimulation by isoriboflavin is less on the peptone medium than on the casein medium, and is decreased by the addition of protein hydrolysate.

1-Ribitylamino-2-amino-4,5-dimethyl-benzene contains only a small part of the riboflavin molecule but acts like isoriboflavin.

Lumiflavin has both an inhibitory and a stimulatory action upon the use of riboflavin for growth. 10 to 300  $\gamma$  of lumiflavin per 10 ml. curtails the slight growth obtained on the basal medium alone, or with small additions of riboflavin. As the amount of riboflavin is increased, a zone is reached where there is no effect of the lumiflavin, and finally in the presence of more riboflavin, lumiflavin has an augmentative effect. Similar experiments with other riboflavin analogues are in progress.

**The isolation of (-)- $\alpha$ -glyceryl-phosphoryl-choline from incubated beef pancreas.** G. SCHMIDT, B. HERSHMAN (by invitation) and S. J. THANNHAUSER. *Boston Dispensary and Tufts Medical School, Boston.* In a comparative study on the enzymatic hydrolysis of phosphatides in various organs it was found that the tissues of the digestive system exhibited by far the greatest activity. In mucosae of the small and large intestines which contained large amounts of phosphatase the phosphatide phosphorus was almost quantitatively transformed into inorganic phosphate, whereas in the mucosa of the stomach and in pancreas the hydrolysis led to the formation of an organic acid-soluble phosphorus fraction. The fraction is soluble in alcohol and is not precipitated from aqueous solutions by heavy metal salts or barium salts. It can be precipitated as a reinecke salt or as a cadmium chloride complex from concentrated alcoholic solutions. On the basis of these properties, a procedure for the isolation of a pure substance was developed.

The product contained nitrogen and phosphorus in equivalent proportions. By acid hydrolysis it was rapidly split into glycerophosphoric acid and choline which quantitatively accounted for the total nitrogen. This behavior is remarkable in view of the behavior of phosphoryl-choline which is very

resistant against boiling mineral acids. The analytical data agree with the assumption that the substance is glyceryl phosphoryl choline.

The substance reacted with periodate in exactly equivalent proportions and was levorotatory ( $\alpha_D^{20} = -5.0^\circ$ ). Thus, it has to be considered as (-)- $\alpha$ -glyceryl phosphoryl choline.

**The liberation of amino acids from animal tissues.** B. S. SCHWEIGERT (by invitation), IRENE TATMAN GREENHUT (by invitation) and C. A. ELVEHIJEM. *Dept. of Biochemistry, Univ. of Wisconsin, Madison.* Studies have been made on the extent of hydrolysis of the protein in animal tissues by acid, alkaline and enzymatic treatments. Microbiological methods were used for the determination of leucine, valine, isoleucine, tryptophane and threonine. The amount of alpha amino N liberated by the digestion methods was determined by the Van Slyke method.

It was found that leucine, valine and isoleucine can be determined satisfactorily after autoelaving for 5-10 hours with 2-5 N HCl or H<sub>2</sub>SO<sub>4</sub>. Tryptophane could not be determined satisfactorily by this method of hydrolysis since low and variable recoveries were obtained.

The use of 3-10 N Ba(OH)<sub>2</sub> as hydrolytic agents was not entirely satisfactory. Recoveries of added tryptophane varied from 20-70 per cent.

Enzymatic digestion with pancreatin was then investigated. When the tissue was homogenized and incubated at 37°C. with pancreatin for 5 days, the alpha amino N values obtained were only 60-70 per cent of those obtained after acid hydrolysis. Similarly, leucine values obtained showed that the digestion was incomplete, since higher values were obtained after acid treatment. Preparations of intestinal mucosa from rat and dog intestines, when added to the digestion mixture with pancreatin were found to increase the alpha amino N, leucine- and tryptophane values as compared to those obtained with pancreatin digestion alone. The alpha-amino nitrogen obtained by a combination of pancreatin and intestinal mucosa was of the same magnitude as that obtained after acid hydrolysis.

**Behavior of wheat starch with enzyme preparations from pancreas and Aspergillus.** SIGMUND SCHWIMMER (introduced by A. K. Balls). *Bureau of Agricultural and Industrial Chemistry, U. S. D. A., Albany, Cal.* The preparations contained alpha-amylase free of maltase and maltase free of amylase respectively. The ratio of initial rates on raw and boiled starch is of one order of magnitude, and increases with increasing amylase concentration. The initial rate varies with the amylase concentration in approximately linear fashion for boiled starch, and as the square root for raw starch. The two enzyme preparations together ultimately convert all of the starch to glucose and maltose, but the maltase preparation has little effect on the

initial rate of sugar formation. Although the quantity of glucose formed is independent of the amount of amylase and varies with the maltase concentration, complete conversion to glucose alone has not been observed. The maltase preparation appears to act with raw and boiled starch similarly, but the former action is more noticeable, as the over-all rate of digestion is increased much more with raw starch. Both maltose and glucose inhibit the action of amylase, and the inhibition is removed by the addition of the maltase preparation. Because of the similarity of inhibition by both sugars, the effect of maltase cannot be explained on the basis of a simple dextrin-maltose equilibrium. A study of possible reactions between glucose and other *Aspergillus* enzymes is indicated. The results show no evidence pointing to an amylase-resistant coating on the starch granule as a major factor responsible for the relatively low susceptibility of raw starch to amylase action. [Part of this work was done on Bankhead-Jones Funds.]

The synthesis of glycine in the rat and guinea pig; conversion of serine to glycine. DAVID SHEMIN. *Dept. of Biochemistry, Columbia Univ., New York.* The synthesis of glycine in the animal organism may involve compounds other than those containing two carbon atoms. In order to investigate the formation of glycine *in vivo*, amino acids and other possible precursors labelled with isotopic nitrogen were injected intraperitoneally into fasting rats and guinea pigs, together with sodium benzoate. From a 24-hour sample of urine, hippuric acid was isolated and the  $N^{15}$  concentration determined. The quotient of the isotope concentration of the injected material by the isotope concentration of the hippuric acid is called the dilution factor. In order to differentiate direct carbon utilization from nitrogen utilization, the dilution factors for isotopic glycine and isotopic ammonia were determined; the latter was considerably higher, indicating relatively little conversion. A dilution factor of magnitude comparable with that for glycine is evidence for the conversion of the test compound to glycine.

In these animals evidence was obtained for the direct conversion of serine to glycine and a possible utilization of L-glutamic acid for the formation of glycine. Negative results were obtained with D-glutamic acid, and L-alanine and L-leucine. The conversion of serine to glycine does not take place through the intermediate of ethanolamine, the dilution factor for which was even higher than that for ammonia. The mechanism for the conversion of serine to glycine is being investigated with heavy carbon. It was found that the guinea pig utilizes ammonia for glycine formation far better than the rat.

Metabolic studies on  $\beta$ -phenylethylamine and some of its derivatives. FRED H. SNYDER (by

invitation), HARTMANN GOETZE (by invitation) and FRED W. OBERST. *Division of Biochemistry, Research Labs., Wm. S. Merrell Co., Cincinnati.*  $\beta$ -Phenylethylamine,  $\beta$ -methyl- $\beta$ -phenylethylamine, N-methyl- $\beta$ -methyl- $\beta$ -phenylethylamine (Voneadrine), N-ethyl-N-methyl- $\beta$ -methyl- $\beta$ -phenylethylamine,  $\alpha$ -methyl- $\beta$ -phenylethylamine (Amphetamine, Benzedrine),  $\alpha$ -methyl- $\beta$ -hydroxy- $\beta$ -phenylethylamine (Propadrine), N-methyl- $\alpha$ -methyl- $\beta$ -hydroxy- $\beta$ -phenylethylamine (Ephedrine), N-ethyl-N-methyl- $\alpha$ -methyl- $\beta$ -hydroxy- $\beta$ -phenylethylamine (Nethamine),  $\beta$ -hydroxy- $\beta$ -phenylethylamine, and  $\beta$ -hydroxy- $\beta$ -methyl- $\beta$ -phenylethylamine have been studied from the standpoints of (1) rate of deamination in the presence of liver amine oxidase and (2) extent of excretion in the white rat following subcutaneous administration.

The conclusions of other workers concerning the relation of structure to susceptibility to oxidation by amine oxidase have been substantially confirmed.

The urinary excretion of compounds that are attacked by amine oxidase is very low. A methyl substituent in the  $\alpha$ -position prevents oxidation by the enzyme and also diminishes destruction of the compound in the body. The introduction of two substituent groups (hydroxyl and methyl) in the  $\beta$ -position increases resistance to enzymatic oxidation and to metabolic breakdown in the intact animal. A tertiary amine, unsubstituted in the  $\alpha$ -position, was excreted in only small amounts although not attacked by amine oxidase.

The apparent conjugation of certain compounds having a hydroxyl group in the  $\beta$ -position has been demonstrated.

The excretion of Nethamine as influenced by feeding a diet containing one or three per cent of ammonium chloride or of sodium bicarbonate has been studied. It was found that larger amounts of the amine are excreted on the acid diet.

The possible relationship of these findings to the mechanism of deamination of amino acids is discussed.

Estimation of calcium in serum before and after electrodialysis. ALBERT E. SOBEL, NATHAN A. SOLOMON (by invitation) and BENJAMIN KRAMER. *Division of Biochemistry and Pediatric Research Lab., The Jewish Hospital of Brooklyn.* Calcium determinations done on the contents of the cathode chamber of electrodialyzed serum, gave consistently higher results than direct precipitation as the oxalate of the same serum. This disagreement may be due to the presence of unionized calcium complexes such as citates, not completely precipitated by oxalate.

To further investigate the problem, known amounts of citrate solutions were added to serum. The pH was adjusted to 5.0 with HCl and calcium

determinations done. The citrated serum gave lower results than the serum directly precipitated. Electrodialysis of the citrated serum, however, gave values higher than the original values obtained on the serum without citrate addition.

Electrodialysis is therefore suggested as a preliminary step in the accurate determination of calcium in serum. The advantages of electrodialysis over ashing or trichloroacetic acid filtrate as the method used are as follows:

1. No loss or splattering as in dry ashing.
2. No addition of reagents which may contain calcium as in trichloroacetic acid precipitation or wet ashing. Also, in trichloroacetic acid precipitation there may be volume changes which are unaccounted for in calculations.

3. Only one anion is present in the electrodialysate which, theoretically, permits the formation of a precipitate of more constant composition.

**Spectrophotometric study of a new colorimetric reaction of vitamin A.** ALBERT E. SOBEL and HAROLD WERBIN (by invitation). *Pediatric Research Lab., Jewish Hospital of Brooklyn.* Spectrophotometric data are presented for the reaction of glycerol 1,3-dichlorohydrin (GDH) with vitamin A and with carotene. GDH possesses two advantages over  $SbCl_3$ : (1) it can be used as it comes from the bottle, and (2) the color produced by its reaction with vitamin A is stable for at least 8 minutes.

Vitamin A reacts with GDH to produce an immediate blue color which has an absorption maximum at  $625 \text{ m}\mu$  and an  $E_{1\text{cm}}^{1\%}$  of 1710. The blue color changes into a more stable (2 to 10 minutes) violet color which exhibits an absorption maximum at  $550 \text{ m}\mu$  and has an  $E_{1\text{cm}}^{1\%}$  of 1240. The violet color obeys Beer's Law up to a concentration of 25 I.U. of vitamin A.

The stability of the violet color permitted the determination to be carried out even in a visual colorimeter.

Vitamin A determinations were performed on several samples of saponified and unsaponified fish liver oils by means of the GDH and  $SbCl_3$  reactions. Agreement between both methods was good.

Carotene reacts with GDH giving a green color stable from 6 to 15 minutes and which has one absorption maximum at  $475 \text{ m}\mu$  and another at  $625 \text{ m}\mu$ .

Interference of carotene upon the reaction of  $SbCl_3$  with vitamin A and the reaction of GDH with vitamin A at the end of 5 seconds (immediate blue color) and at the end of 6 minutes (stable violet color) were investigated. The carotene interference was least in the GDH reaction at the end of 5 seconds.

**Distribution of ketone bodies in the organism.** MICHAEL SOMOGYI and IRENE E. STARK (by invitation). *Jewish Hospital, St. Louis.* Beta-hydroxy-

butyric acid and acetoacetic acid were determined in the liver, muscle and blood of healthy rabbits. Because of the very small amounts of ketone bodies in well fed animals, procedures had to be elaborated for the microanalysis of muscle and liver. The customary techniques yield grossly distorted results.

Our findings are: 1. The concentration of total ketone bodies is considerably higher in the liver than in the other tissues; between blood and muscle there is little difference. 2. In the liver, over 90 per cent of the ketone bodies is  $\beta$ -hydroxybutyric acid; the slight, sometimes negligible, amounts of acetoacetic acid are probably in the fluids of the extracellular spaces. In blood and muscle acetoacetic acid is roughly one-third of the total ketone bodies.

These facts suggest that since the liver cells, the site of origin of ketone bodies, contain virtually no acetoacetic acid,  $\beta$ -hydroxybutyric acid is the mother substance that is formed in the oxidation of fatty acids and amino acids. The reversible conversion to acetoacetic acid, then, takes place in the extrahepatic tissues.

**The determination of choline via its reineckate.** WARREN M. SPERRY and FLORENCE C. BRAND (by invitation). *Dept. of Biochemistry, New York State Psychiatric Inst. and Hospital, New York.* A modification of the oxidizing and color-developing procedures of Marenzi and Cardini (*J. Biol. Chem.*, 147: 363 (1943)) was employed in determining the solubility of choline reineckate in various solvents at  $0^\circ$  and room temperature. The results indicate that considerable losses in the solvents used for washing the precipitated choline reineckate may occur under the conditions of several published methods for choline determination. In the Marenzi-Cardini procedure this solubility is greater than the choline reineckate equivalent of the smaller quantities of choline which, the authors state, can be determined with their method. In other methods where the minimal amounts of choline determined are much higher this potential error is much less, but it is by no means negligible, being about 30 per cent in some cases. The good results which have been reported probably represent an approximate compensation between solubility losses and reinecke salt which is not washed out.

The solubility of choline reineckate in the butanols is very small, while the solubility of specially purified reinecke salt is sufficiently large to permit their use as solvents in the determination of choline via the reineckate. With a combination of secondary and tertiary butanols it is possible to determine as little as 10 micrograms of choline. A brief description of the procedure will be given.

**Spectrophotometry of cerebrospinal fluids following concussion.** M. SPIEGEL-ADOLF, G. C.

HENNY (by invitation), H. T. WYCIS (by invitation) and E. SPIEGEL. *Dept. Colloid Chemistry and Exp. Neurology, Temple Univ. School of Medicine, Philadelphia.* An attempt has been made to find in the cerebrospinal fluid (csf), following cerebral concussion, a correlate to cellular changes in the central nervous system. The esf's were studied spectrophotometrically in patients who had sustained a concussion as well as in cats and dogs in which acceleration concussion has been produced by means of graded blows produced by a pendulum. In both series, the esfs showed an absorption band in ultraviolet light with a peak at about 2650 Å, besides the normal end absorption. This change was demonstrable within a few hours following the cerebral trauma and persisted for more than a week. It was observed while the protein content of the esf was normal and in the absence of blood. Barbiturates, the absorption bands of which interfere, were avoided. Since purin and pyrimidin groups give similar absorption bands, the presence of cleavage products of nuclear substances in the csf seems probable. This assumption is supported by the fact that nerve cells in the state of chromatolysis show changes in concentration of ribonucleotide (Gersh and Bodian), and that chromatolysis is found in various parts of the cerebrum following concussion (Magoun and Windle). Similarly, as in our study of esf's following electrically induced convulsions (These Proceedings, Spiegel-Adolf and Spiegel), spectrophotometry permits one to detect in the esf substances indicating cellular injury in the central nervous system. This method may be an aid in the differential diagnosis of organic changes and functional disorders in cases of head trauma. [Aided by grant from the J. and M. Markle Foundation.]

**X-ray diffraction studies on fish bones.** M. SPIEGEL-ADOLF and G. C. HENNY (by invitation). *Dept. of Colloid Chemistry and Physics, Temple Univ. School of Medicine, Philadelphia.* In systematic x-ray diffraction studies of bones, fish bones were used to good advantage because of the relative thinness and moderate x-ray opacity of these structures. Both unchanged and decalcified bones were used. For these studies a cylindrical camera of a 50.8 mm. radius was constructed. The specimen is rotated around its longitudinal axis which is parallel with the slit of the diaphragm. Besides, the usual flat cameras were used.

An x-ray diffraction study of the non-decalcified fish bones shows a pattern rich in lines. The three most prominent ones in decreasing sequence of intensity correspond to spacings of 2.73, 1.76, 2.22 Å. These and other spacings are in good agreement with findings of Reed and Reed (Am. J. Physiol. 138: 34, 1942) in rat bone and apatite. Existing small variations may be accounted for by existing differences in the chemistry of fish bones

(Hammarsten). After decalcification the previously observable orientation becomes more plainly manifest. In a lower rib which apparently has to resist lateral pressure, the x-ray diffraction pattern of the decalcified rib is practically identical with the pattern of the tendon. Astbury has shown in keratin that a sidewise acting squeeze has an effect similar to stretching. In an upper rib (clavus) in which the pressure acts mostly against the longitudinal axis only one pair of orientation points is detectable. They become weaker when the rib is stretched under weight, confirming thus the assumed direction of stress. After boiling, a marked sharpening of the back bone reflection becomes manifest, while the x-ray diffraction pattern of the calcified bone remains unchanged.

**Spectrophotometric findings in cerebrospinal fluid following electrically induced convulsions.** M. SPIEGEL-ADOLF and E. SPIEGEL. *Dept. of Colloid Chemistry and Experimental Neurology, Temple Univ. School of Medicine, Philadelphia.* Continuing our studies (Fed. Proc. 3: no. 1, 1944) on the effect of electrically induced convulsions upon the cerebrospinal fluid in dogs, we found in spectrophotometric studies, before the convulsions and absorption only. Following a series of 5-7 convulsions at 2-3 day intervals, there was regularly an absorption band between wave length 2550 and 2850 Å (maximum between 2650 and 2700 Å). Since an abnormal protein content could be excluded, and barbiturates had not been administered to the dogs, the absorption band probably is due to abnormal amounts of nucleic acids or their constituents, belonging to the pyrimidine-purine group. While uric acid was not increased, traces of thymonucleic acid were detected by Disehe's diphenylamin method in the cerebrospinal fluid following the convulsions. These findings suggest a breakdown of nuclear substances under the influence of the convulsions, as indicated by histologic studies.

**Chromosin. I. On the size and shape of the particles in solution.** KURT G. STERN, RUTH BELOFF (by invitation) and SANFORD DAVIS (by invitation). *Dept. of Chemistry, Polytechnic Inst., Brooklyn.* The desoxyribonucleoprotein (*chromosin*) contained in the nuclei of avian erythrocytes was isolated essentially according to Mirsky and Pollister (Trans. N. Y. Acad. Sci. Ser. II, 5: 190 (1943)). The extraction, purification, and all subsequent measurements were performed on 1 M. NaCl solutions of the protein.

Chromosin prepared in this manner was found to be monodispers and homogeneous upon ultracentrifugal and electrophoretic examination. It was free of hemoglobin. The material sedimenting with a sharply-defined boundary at high dilution (0.06 per cent) had a sedimentation constant of 31 Svedberg units. The diffusion constant at the

same concentration was found to be  $D_{200} = 1 \times 10^{-7}$  cm<sup>2</sup>/sec. The insertion of these constants in Svedberg's equation yields a molecular weight for this component of  $2.2 \times 10^6$ . The frictional ratio,  $f/f_0$ , equals 2.5, indicating an axis ratio of 35:1.

The above values are very similar to those reported by Carter (J. Am. Chem. Soc. 63: 1960 (1941)) for calf thymus nucleohistone, but they are sufficiently different from those reported by Tennent and Vilbrandt (*ibid.* 65: 424 (1943)) for sodium thymonucleate to render it unlikely that the sedimenting boundary observed in strong salt solutions in the present experiments is due to free thymonucleic acid rather than to the intact nucleoprotein.

Chromosin shows a strong absorption maximum in the ultraviolet region of the spectrum, centered at 2600 Å. [This work was aided by a grant from the Carrie S. Schuer Foundation of New York City.]

**Chromosin. II. Rheological properties.** KURT G. STERN, S. C. SHEN (by invitation) and PAT MACALUSO (by invitation). *Dept. of Chemistry, Polytechnic Inst., Brooklyn.* The viscosity of chromosin solutions, prepared from the nuclei of avian erythrocytes, was studied at various concentrations and velocity gradients, using Ostwald viscosimeters. Dilute solutions of this nucleoprotein in 1 M. NaCl exhibit a high viscosity (e.g.  $\eta_{sp.} = 8.57$  at 0.5 per cent protein concentration). Upon increasing the air pressure on the viscosimeter the viscosity decreases markedly: from 8.57 at atmospheric pressure to 4.8 at 18 mm. Hg additional pressure, at 30°. This behavior is characteristic of particles possessing a high degree of asymmetry.

The addition of 1 part of a cationic detergent (benzyl trimethyl alkyl ammonium chloride) to 1.25 parts of chromosin produces an immediate increase of 50 per cent in the relative viscosity which then remains unchanged for over 16 hours.

Chromosin solutions, when examined between crossed Nichols while being subjected to various shearing stresses, exhibit a marked double refraction of flow. The extinction angle approaches zero at relatively low shear forces, thereby indicating a high degree of orientation of the elongated particles.

Chromosin and chromosin-cationic detergent mixtures, when extruded from a spinnerette into distilled water yield fibers exhibiting considerable strength and a negative birefringence. The x-ray diffraction patterns obtained with such fibers and with chromosin solutions while flowing through capillaries are being studied in this laboratory by Dr. I. Fankuchen and Mrs. R. Beloff. [This work was aided by a grant from the Carrie S. Schuer Foundation of New York City.]

**Carbohydrate metabolism studied with the aid of deuterium.** DEWITT STETTEN, JR., GEORGE E. BOXER and BABETTE KLEIN (by invitation). *Dept.*

*of Biochemistry, College of Physicians and Surgeons, Columbia Univ., New York.* In continuation of previously published work (*J. Biol. Chem.* 155: 231, 237, 1944; *ibid.* 156: 271, 1944), the uptake of deuterium from body water into glycogen of liver and muscle of rats has been studied under various conditions of diet and disease. Reasoning from postulates previously laid down, it could be shown from the isotope data that the glycogen deposited in the liver of the previously fasted rat in response to adrenalin was derived from blood lactate, in confirmation of the work of Cori.

The glycogen synthesized in liver and in muscle by the previously fasted rat given insulin parenterally and glucose by stomach tube was poor in deuterium, indicating that the process of glycogenesis favored by insulin was the direct coupling of hexose molecules. The glycogen deposited by diabetic rats was rich in deuterium and is believed to be formed in good part from fragments smaller than hexose.

The depression of lipogenesis in the (alloxan) diabetic rat has been confirmed, this time in a rat receiving alanine instead of glucose. No such marked depression of fatty acid synthesis occurred in the phlorhizinized rat. Comparison of the deuterium contents of the urinary glucose obtained from the phlorhizinized and alloxan-poisoned rats revealed that the quantity of glucose synthesized in vivo in the animal deficient in insulin, poisoned with alloxan, was no greater than the corresponding quantity in the phlorhizinized rat, presumed to have normal islet tissue.

**Pyruvic oxidase of *proteus vulgaris*.** P. K. STUMPF (introduced by D. E. Green). *Dept. of Medicine and Biochemistry, College of Physicians and Surgeons, Columbia Univ., New York.* *Proteus vulgaris* contains an enzyme which catalyzes the oxidation of pyruvic acid to acetic acid and CO<sub>2</sub>. For every molecule of pyruvic acid oxidized, one atom of oxygen is consumed and one molecule each of acetic acid and CO<sub>2</sub> are formed. The enzyme appears to be a complex consisting of (1) a specific protein, (2) diphosphothiamin, and (3) a divalent metal, probably magnesium. As prepared, the enzyme is partially dissociated and requires the addition of both diphosphothiamin and some divalent metal to attain maximum activity. The intact bacterial cell contains a phosphatase which can split diphosphothiamin to thiamin. This phosphatase, although absent in the final preparation of pyruvic oxidase, may well account for the splitting off of diphosphothiamin from pyruvic oxidase.

The pyruvic oxidases of *Proteus vulgaris* and *Escherichia coli* appear not to require inorganic phosphate for activity. Moreover, in the presence of 0.1 M phosphate, acetyl phosphate is not formed. Pyrophosphate in  $3.4 \times 10^{-3}$  M concentration inhibits the enzyme activity completely but this

inhibition is reversed by  $0.7 \times 10^{-3}$  M diphosphothiamin.

The enzyme is obtained by disintegrating cells of *Proteus vulgaris* with ultrasonic vibrations, by separating the juice from intact cells and cellular debris through fractional centrifugation, and finally by precipitating with acetic acid. The enzyme is associated with macroparticles which can be sedimented in strong gravitational fields.

Studies on phosphatase-containing enzyme preparations for hydrolysis of cocarboxylase in brewers' yeasts and wheat embryo. BARNETT SURE. *Dept. of Agricultural Chemistry, Univ. of Arkansas, Fayetteville*. Optimum pH. Two brewers' type yeasts were used containing 50 to 60 per cent of their thiamine in combined form. Maximum yields were not obtained until the pH was at least 4.4 in order to activate the cocarboxylase hydrolyzing phosphatase. On the other hand, in commercial wheat embryo, containing about 40 per cent combined thiamine, over 90 per cent of maximum yields were obtained at as low a pH as 2.0. These results suggest that cocarboxylase may exist in different combinations in various foods or food-products.

*Relative efficiency of various commercial preparations.* Takadiastase, clarase, polidase, and mylase were used in 10, 1, and 0.1 per cent concentrations as sources of phosphatase for hydrolyzing cocarboxylase in brewers' type yeasts. Polydase was the poorest and takadiastase and mylase were found to be the most potent sources.

*Destruction of phosphatase in dilute acid.* Three minutes contact of the cocarboxylase hydrolyzing phosphatase contained in commercial preparations is destroyed at a pH of 1.8 but is uninjured at a pH of 2.2, when used on brewers' type yeasts.

Intestinal synthesis of nicotinic acid and "folic acid" in rats on various diets. LESTER TEPLY (by invitation), WILLARD KREHL (by invitation) and C. A. ELVEHJEM. *Dept. of Biochemistry, Univ. of Wisconsin, Madison*. Several attempts to produce a nicotinic acid deficiency in the rat through suppression of the intestinal flora have been unsuccessful. Dann (J. Biol. Chem. 141: 803, 1941) has concluded that the rat does not depend on intestinal synthesis for its nicotinic acid. The problem was attacked by first determining which diets (carbohydrate changes in particular) cause the least amount of synthesis of nicotinic acid in the gut. With this information at hand, highly purified rations were prepared to which sulfasuxidine or sulfaphthalidine were added at levels up to 4 per cent. The growth of rats on these diets, which contained a specially prepared norite eluate from solubilized liver extract to supply "folic acid," was markedly inferior to the growth obtained on the same diets with added nicotinic acid.

Microbiological assays were used for the estima-

tion of nicotinic acid and "folic acid" in the cecal contents of the rats which had been on certain diets for varying periods of time. Dextrin and lactose caused greater production of nicotinic acid and "folic acid" than glucose or sucrose. Inclusion of 15 per cent skim milk powder in the sucrose basal ration caused a marked increase in the "folic acid" content of the intestinal contents; the addition of sulfasuxidine reduced the "folic acid" content to that obtained with the sucrose basal ratio plus sulfasuxidine. On skim milk powder rations, the type of fat added markedly affected the amount of nicotinic acid produced in the cecum.

Molecular weights of liver glycogen from animals fed glucose and galactose. FRANK K. THOMPSON (by invitation) and EDWARD S. WEST. *Dept. of Biochemistry, Univ. of Oregon Medical School, Portland*. Bell (Biochem. J. 30: 1612, 1936), from data by Haworth's methylation end-group assay method, concluded that rabbit liver glycogen formed from galactose is composed of 18 glucose units while that from glucose contains only 12 units per molecule. Meyer (Helv. Chim. Acta, 24, 375 (1941) considers glycogen to consist of branched aggregates of glucose, in which case Haworth's method would be invalid.

Liver glycogen from rabbits and rats fed galactose and glucose according to Bell, was prepared according to Bell's method, with subsequent electrodialysis.

The molecular weights of the above glycogens were obtained by permanganate oxidation in 1:1  $H_2SO_4$  at 90–95°C by potentiometric titration of 10 mg. samples of glycogen and of glucose. If  $R$  = weight of permanganate for oxidation of glycogen divided by permanganate for oxidation of glucose,  $M_p$  = molecular weight of glycogen,  $M_m$  = molecular weight of glucose, then the molecular weight of glycogen is calculated by the equation:—

$$M_p = M_m \left( \frac{R}{9.9964 - 8.9964 R} \right) - 18.016 \left( \frac{R}{9.9964 - 8.9964 R} - 1 \right)$$

Eight samples of glucose required an average of 27.332 mg. of  $KMnO_4$  for oxidation. Thirteen samples of glycogen from galactose rats required 30.223 mg. Ten samples from galactose-rabbits required 30.221 mg. Galactose-glycogen molecular weight was 3,746, representing 23 glucose units.

Six glycogen samples from glucose-rats required 30.225 mg. of  $KMnO_4$ , and ten samples from glucose-rabbits required 30.211 mg. Glucose-glycogen molecular weight was 3,584 representing 22 units.

*Preparation of glycolytic extracts and homogenates from brain and cord.* MERTON F. UTTER and JOHN M. REINER (introduced by Harland G.

Wood). *Dept. of Physiology, Univ. of Minnesota, Minneapolis.* An investigation of the means for preparing and testing brain and spinal cord homogenates and extracts (centrifuged homogenates) has been carried out with the ultimate aim of using such systems for the assay of glycolytic enzymes.

Brain extracts have been previously reported to contain an inhibitor whose activity was intensified by increasing enzyme concentration or by prolonging the reaction time (Geiger, *Biochem. J.* 34: 465, 1940). This inhibitor has been found to be a nucleotidase which inactivates diphosphopyridine nucleotide (DPN). Inactivation can be prevented by addition of nicotinamide or by incubating the extract with DPN and NaHCO<sub>3</sub> previous to the start of the reaction.

With proper additions, homogenates have been obtained from both brain and cord of rats which exhibit QCO<sub>2</sub> values of 50-75 and 40-50 respectively as compared with values of 30-50 for brain extracts and 25-35 for cord extracts. For maximum activity of homogenates and extracts the following components, in addition to glucose and buffers, must be added: hexosediphosphate, adenosinetriphosphate, MgCl<sub>2</sub>, DPN, and nicotinamide. The QCO<sub>2</sub> values of fortified homogenates far exceeds glycolytic rates reported for brain homogenates in which no provision for addition of substances other than substrate, salts, and buffer (Racker and Kabat, *J. Exp. Med.* 76: 579-585, 1942) have been made. The very small fraction of the potential activity exhibited by such preparations invalidates any attempt to use unfortified homogenates in the assay of glycolytic enzymes since enzyme concentrations will not be limiting factors.

**Excretion of urinary corticoid hormones.** ELEANOR H. VENNING and J. S. L. BROWNE. *McGill Univ. Clinic, Royal Victoria Hospital, Montreal.* Excretion of corticoid hormones as measured by glycogen deposition in the liver of fasted adrenalectomized mice has been studied in patients following damage and in various endocrine disturbances. The standard used at present is the Adrenal Cortical Extract of the Connaught Laboratories and the urinary biological activity is expressed in terms of equivalent activity of cc. of this extract.

It has been found that acidification of the urine to pH 1 prior to extraction greatly enhances the biological activity. Under these conditions normal males excrete an average of 0.65 cc. and normal females 0.30 cc. per day.

In two cases of Addison's Disease no urinary corticoid activity was found. In one case of Simmond's Disease the urine contained no detectable biological activity, however following the administration of corticotrophin over a period of 3 days, the equivalent of 0.39 cc. per 24 hours were excreted.

In one case of anorexia nervosa the urine con-

tained normal amounts. Six cases of essential hypertension were investigated (3 males and 3 females), but no increase in the excretion of corticoid hormones could be detected.

Following severe burns in 3 cases, there was an immediate rise in urinary corticoid activity which in one of the cases reached a level ten times the normal value. This excretion remained high for approximately 3 weeks and then fell to normal levels.

Four cases of damage caused by an exploding mortar were followed over a period of several weeks. The urinary activity rose abruptly in response to damage and remained high.

**The antiscorbutic properties of 3-methyl ascorbic acid.** CARL S. VESTLING and MILDRED C. REB STOCK (introduced by W. C. Rose). *Division of Biochemistry, Univ. of Illinois, Urbana.* In connection with a study of certain ascorbic acid derivatives, the antiscorbutic properties of 3-methyl ascorbic acid have been reinvestigated (Bezsonov, N., and Saerez, R., *Compt. rend. soc. biol.*, 124: 356 (1937)).

Young male guinea pigs have been used in the experiments to be reported, and both the protective and the curative techniques have been employed. In these experiments scorbutogenic diets have been supplemented by either pure, crystalline 3-methyl ascorbic acid or by ascorbic acid.

The results indicate that 20 mg. per day of 3-methyl ascorbic acid will protect guinea pigs on a scorbutogenic ration against scurvy and will result in essentially normal growth. This amount is also effective in curative experiments. Smaller doses result in diminished responses. It is of interest to note that similar results have been obtained whether the compound has been fed or injected intraperitoneally.

It is apparent that only a small fraction of the 3-methyl ascorbic acid is available to the guinea pig, irrespective of the mode of administration. After injection excretion by the small intestine cannot be excluded. It seems reasonable to suggest that limited hydrolysis takes place either in the intestine or in the tissues, and that the unhydrolyzed material is excreted in the urine. Experiments designed to investigate this aspect are now in progress.

**A chemical method for the determination of glutamic acid.** HEINRICH WAELSCH and BLANCHE A. PRESCOTT (by invitation). *Dcpt. of Biochemistry, New York State Psychiatric Inst. and Hospital, New York.* Glutamic acid is the only known amino acid which under the action of ninhydrin is converted into an acid aldehyde: formyl propionic acid. In the method to be described this aldehyde is coupled with 2,4-dinitrophenylhydrazine and the acid hydrazone is extracted into an organic solvent and reextracted with carbonate solution.

The reddish-brown color, which develops on the addition of alkali, is read in the colorimeter. In the range studied corresponding to 5-50 $\gamma$  of glutamic acid, the color developed by the synthetic hydrazone obeys Beer's law. Ring formation of the hydrazone in acid solution, its stability in aqueous solutions over a range of pH values, and its distribution between aqueous solutions and organic solvents were studied. Of the other amino acids tested only aspartic acid gives an acid hydrazone in varying yield, probably by a secondary reaction. The separation of the hydrazones was attempted without success by distribution between different solvents, by varying the pH and by chromatographic analysis. The separation in the range of 10 to 50 $\gamma$  of glutamic acid from aspartic acid and other amino acids was accomplished by adsorption on aluminum oxide and elution with acetic acid.

**Significance of the effects of x-ray on lymphoid tissue.** ABRAHAM WHITE and THOMAS F. DOUGHERTY (by invitation). *Dept. of Physiological Chemistry and Anatomy, Yale Univ., New Haven.* The similarity in the effects of x-rays<sup>1</sup> and of pituitary-adrenal cortical secretion on numbers of blood lymphocytes<sup>2</sup> and lymphoid tissue<sup>3</sup> suggested the possibility that X-rays acted via the pituitary-adrenal cortex relationship.

CBA mice, 60 to 80 days old, received total body radiation. A large dose (200 r) produced, within 3 hours, decrease in adrenal cholesterol, lymphopenia, tissue lymphocyte degeneration, and total serum protein and gamma globulin increases. These changes also occurred in one day post-operative adrenalectomized mice receiving 200 r. This dose also gave an anamnestic response in previously immunized mice in the absence of the adrenals.

It was found that 10 r produced the same physiological alterations, including the anamnestic response, in normal, but not in adrenalectomized, mice. Therefore, 10 r influence lymphoid tissue function by augmenting pituitary-adrenal cortical secretion. Large doses may produce lymphocyte degeneration without endocrine mediation.

The release from lymphocytes of gamma globulin<sup>4</sup> and antibodies<sup>5</sup> is under pituitary-adrenal cortical control. Large radiation doses directly release lymphocyte protein without this endocrine mediation. This is further proof that adrenal steroids produce hyperglobulinemia by their degenerative actions on lymphocytes.

<sup>1</sup> Downey, H. *Handbook of Hematology*, vol. 4, chapter 39. Paul B. Hoeber, Inc., New York, 1938.

<sup>2</sup> Dougherty, T. F. and A. White. *Endocrinology* 35: 1, 1944.

<sup>3</sup> White, A. and T. F. Dougherty. *Proc. Soc. Exper. Biol. and Med.* 56: 26, 1944.

<sup>4</sup> White, A. and T. F. Dougherty. *Abs. Proc. Am. Chem. Soc.*, New York, Sept. 1944; *Endocrinology*, in press.

<sup>5</sup> Dougherty, T. F., J. H. Chase and A. White. *Proc. Soc. Exper. Biol. and Med.* 57: 295, 1944.

**The effect of diet on the basal metabolic rate of mice.** FLORENCE R. WHITE (introduced by Jesse P. Greenstein). *National Cancer Inst., Bethesda, Md.* A diet sufficiently restricted in cystine to keep weanling mice from growing, has been shown to change the incidence of spontaneous mammary tumors in strain C3H female mice from 97 per cent to zero.<sup>1</sup> Later work<sup>2</sup> showed that this suppression of tumor formation was due to lack of estrus.

Mice fed the low cystine diet from weaning were always small, and might be said to appear stunted. Since sexual activity is abolished by underfeeding, and since inanition is also accompanied by a lowering of the basal metabolic rate, it seemed possible that such mechanisms might be operating in these mice. Accordingly the basal rate of oxygen utilization of strain C3H virgin female mice was determined with Mitchell's modification of Haldane's open circuit apparatus.<sup>3</sup> The mice had been fed either the low cystine diet, or the same ration supplemented by cystine for from 3 to 15 months before the basal metabolic rates were determined. Results show that the rate of oxygen consumption is essentially the same in the two groups.

**Proteins in chylous ascitic fluids and the possible relationship to the origin of plasma proteins.** VERNON A. WILKERSON. *Dept. of Biochemistry, Howard Univ. School of Medicine, Washington.* The fluid from two cases of chylous ascites was studied. This is a rare condition caused by the obstruction or injury of the receptaculum chyli or the thoracic duct and offers an opportunity to study certain characteristics of chylous fluid.

The fluid contained 2.01 per cent of total protein which, upon isolation, was found to be a globulin. The isoelectric point of the protein was at pH 4.6 and its nitrogen distribution agreed favorably with the nitrogen distribution of the globulin of blood plasma. More significant was the total absence of albumin. In previous studies the proteins of chylous ascitic fluids were characterized as albumins on the basis of coagulability.

The presence of globulin in this fluid and the total absence of albumin, a more diffusible molecule, gives additional evidence to support the theory that the globulin of the blood plasma is derived from the reticuloendothelial system of the lymph nodes and is supplied to the blood stream through the thoracic duct.

The presence of globulin and the absence of albumin also offers a method of distinguishing true chylous ascites from pseudochylous ascites.

The specific gravity, ash, fat and carbohydrate contents of the fluid were determined.

<sup>1</sup> J. White and H. B. Andervont. *J. Nat. Cancer Inst.* 3: 449, 1943.

<sup>2</sup> F. R. White and J. White. *J. Nat. Cancer Inst.* 4: 413, 1944.

<sup>3</sup> H. H. Mitchell and G. G. Carmen. *Am. J. Physiol.* 76: 385, 1926.

Position of heavy carbon, fixed from sodium bicarbonate, in glucose from rat liver glycogen. HARLAND G. WOOD, VICTOR LORBER and NATHAN LIFSON. *Dept. of Physiology, Univ. of Minnesota, Minneapolis.* The glycogen of rat liver was isolated following intraperitoneal administration of heavy carbon bicarbonate and feeding of glucose by stomach tube. The position of the labelled carbon in the glucose from the glycogen was determined by bacterial and chemical degradation. Lactic acid from the bacterial fermentation was oxidized with permanganate to acetaldehyde and carbon dioxide. The acetaldehyde was further degraded by the iodoform reaction to iodoform and formic acid. By this method carbons number 1 and 6, 2 and 5, and 3 and 4 of the glucose were obtained as separate fractions. The chemical degradation involved con-

version of the glucose to methyl glucoside and oxidation with periodic acid. Carbon number three was split out as formic acid leaving a methylated dialdehyde. The dialdehyde was then hydrolyzed and oxidized with periodic acid giving carbon number six as formaldehyde and carbons 1, 2, 4, and 5 as formic acid.

The results show that carbon dioxide carbon is fixed in positions three and four of the glucose and that the concentration of C<sup>14</sup> is probably equal in each position. These observations are in accord with, but do not necessarily prove the mechanism of glycogen synthesis as proposed by Solomon *et al.* (*J. Biol. Chem.* 140: 171 (1941)). The C<sup>14</sup> distribution in the glucose and in the lactic acid obtained by bacterial degradation of this glucose is consistent with that predicted by current concepts of glycolysis.

## THE AMERICAN SOCIETY FOR PHARMACOLOGY AND EXPERIMENTAL THERAPEUTICS

Abstracts of papers presented for the annual meeting scheduled for Cleveland, May 8, 9, 10, 1945. On account of the cancellation of this meeting, all the papers are to be regarded as "read by title". For possible correction in any of the abstracts see the next issue.

**Pharmacological effects of  $\beta$ -piperidinoethyl  $\alpha$ -methyl-p-xenylacetate HCl,  $\beta$ -diethylaminoethyl phenyl- $\alpha$ -thienylacetate HCl and  $\beta$ -diethylaminoethyl phenyl- $\alpha$ -thienylglycolate ( $\alpha$ -thienylhydroxyacetate) HCl.** BENEDICT E. ABREU and ELIZABETH TROESCHER-ELAM (by invitation). *Division of Pharmacology and Experimental Therapeutics, Univ. of California Medical School, San Francisco.* By means of tandem balloons and Harvard membrane manometers, studies on colonic spasmolysis were made on 5 unanesthetized dogs, 12 rabbits anesthetized with 2.0 cc./kg. paraldehyde, intragastrically, and 4 monkeys (*Macacus rhesus*) premedicated with 20 mgm./kg. sodium pentobarbital, intraperitoneally. Morphine was employed as the spasmogenic agent in dogs and monkeys, and pilocarpine in rabbits. Additional observations were made on: (1) such parasympatholytic effects as are evidenced by cardiae acceleration, mydriasis and cycloplegia and (2) central nervous system activity.

In dogs and rabbits, spasmolysis was produced by 0.1 mgm./kg. I.V. doses of the p-xenylacetate and  $\alpha$ -thienylacetate for 3 to 7 minutes and by 0.1 mgm./kg. I.V. doses of the  $\alpha$ -thienylglycolate for 15 to 30 minutes.

Since  $\beta$ -diethylaminoethyl phenyl- $\alpha$ -thienylglycolate was found to be most active, it was subjected

to more intensive investigation. Administered subcutaneously in 1 mgm./kg. doses to dogs, it was spasmolytic for 30 to 135 minutes. Repeated administration resulted in tachyphylaxis in 2 dogs. Duration of spasmolysis was approximately 3 times longer than that elicited by comparable dosage of  $\beta$ -diethylaminoethyl diphenylacetate HCl (trasentin) and  $\beta$ -diethylaminoethyl fluorescein-9-carboxylate HCl (pavatrine). In monkeys, identical dosage of the thienylglycolate produced spasmolysis lasting from 18 to 113 minutes without tachyphylaxis.

No appreciable change in cardiac rate was noted in monkeys. In dogs, an acceleration of from two to four times the control value occurred. Mydriasis was observed in dogs and rabbits and cycloplegia in dogs. Neither was produced in monkeys. Dogs were markedly excited and ataxic for 1 to 3 hours, while monkeys, rabbits and rats were not.

Monkeys were quieted by single or repeated dosage. In one monkey, 64 mgm./kg. intramuscularly was lethal, indicating a margin of safety comparable to that of atropine given intravenously to rabbits and dogs. [Supported in part by a grant from Frederick Stearns & Company.]

**The cutaneous vasodilating action of pitressin.** RAYMOND P. AHLQUIST (by invitation) and ROBERT A. WOODBURY. *Dept. of Pharmacology, Univ. of Georgia School of Medicine, Augusta.* The vaso-

constricting action of Pitressin (as shown by its pressor action and coronary constricting effect) is well known. Reference to its vasodilating action has not been reported even though cutaneous flushing is occasionally encountered in patients. The action of Pitressin to produce first an arterial shift (increased oxygen and decreased carbon dioxide content) in femoral venous blood of the dog followed by a venous shift (decreased oxygen and increased carbon dioxide content) is indicative of a vasodilating action of the drug.

The present, accepted explanation for these actions are that Pitressin interferes with oxidative enzymes but the following results show that these effects are due to circulatory changes.

Blood pressure, bubble flowmeter and  $\text{CO}_2$  and  $\text{O}_2$  venous blood determinations in dogs with the skin removed from one leg show that in the skinless leg, Pitressin reduces the blood flow much more than in the normal control leg and that the skinless leg shows only a venous shift while simultaneously the normal control leg shows the characteristic arterial shift followed by the venous shift.

Repeated doses of Pitressin (every 10 minutes) result in only a venous shift after about the seventh dose. Also tachyphylaxis may develop to an animal's own vasopressin since dogs in poor condition do not show an arterial shift.

Coronary venous blood shows only the venous shift.

The femoral venous blood of the rabbit shows only the venous shift following Pitressin while Metabolic studies indicate a decreased oxygen consumption.

It is concluded from these data that Pitressin constricts muscle vessels and dilates certain skin vessels. This results in a greatly decreased total blood flow in the leg but the blood that does return in the femoral vein is at first chiefly from the skin areas where vasodilation is occurring. As the cutaneous vasodilation disappears the femoral blood then becomes more venous due to the relative increase in amount of very venous blood from the muscles. This study was partially supported by a grant from Eli Lilly & Co.

Para-aminobenzoic acid: its action on experimental spotted fever. LUDWIK ANIGSTEIN and MADERO N. BADER (introduced by Chauncey D. Leake). Dept. of Preventive Medicine, Univ. of Texas, Medical Branch, Galveston. On the basis of favorable results in the treatment of rickettsial infections with p-aminobenzoic acid (Yeomans, Snyder et al., J. A. M. A. 126: 349, 1944; Greiff, Pinkerton and Moragues, J. Exper. Med. 8b: 561, 1944) this compound was tried on guinea pigs infected with a spotted fever strain of high virulence. 3 gms of PABA were added to each 100 gms of feed. This mixture was found toxic but when reduced to 2 gms of PABA per 100 gms of high

protein diet it was well tolerated and proved effective. Several series of guinea pigs were treated by this PABA mixture prior to the infection while in others the PABA intake started at the time of intraabdominal injection of the virus. Feeding with PABA was continued for ten subsequent days or longer.

As compared with control animals which after 3-4 days of incubation developed high fever lasting for 6-7 days or died during the disease, the great majority of test guinea pigs remained afebrile or developed slight fever of one day duration after the usual incubation. These preliminary experiments seem to indicate that it is possible to prevent spotted fever in guinea pigs pretreated by PABA or to reduce the infection to an abortive stage when PABA is given during the incubation period.

Blood changes in the albino rat following administration of reticulo-endothelial immune serum (Reis). LUDWIK ANIGSTEIN (by invitation) and CHARLES M. POMERAT, Deps. of Preventive Medicine and Anatomy, Univ. of Texas Medical Branch, Galveston. Spleen and bone-marrow from albino rats were repeatedly injected into rabbits with the object of preparing reticulo-endothelial immune serum (REIS). Rats of local stock were injected intra-abdominally with a single dose of 0.5 cc. of undiluted homologous REIS and blood counts were taken every 24 hours. In contrast to controls receiving the same amount of normal rabbit serum, test animals showed a rapid decline in erythrocytes and hemoglobin, in some cases from 9 million red cells to 3 million. The loss of hemoglobin was even more striking. Evidently, REIS at strong concentrations exerts a damaging effect on hemopoiesis. These results are consistent with similar inhibitory action of REIS on tissue grown *in vitro* (Pomerat and Anigstein, Science, 100: 456, 1944; also Pomerat and Anigstein, Texas Rep. Biol. and Med., 1945, in press).

Minute, extra- and intracellular bodies were demonstrated in blood films from some rats with severe anemia. Since the original rats were not bartonella free it is possible that in these cases an acute bartonellosis was produced as result of blockade of RES by REIS.

The *in vitro* effects of atabrine and two of its derivatives upon the acid fast bacilli. ROY C. AVERY and CHARLOTTE B. WARD (both introduced by Paul D. Lamson). Deps. of Pathology and Pharmacology, Vanderbilt School of Medicine, Nashville, Tenn. An investigation was made of the *in vitro* effects of atabrine, 2-methoxy-6-chloro-9-( $\gamma$ -n-piperidylpropyl-amino) acridine dihydrochloride and 2-methoxy-6-chloro-9-( $\delta$ -diethylamino butyl-amino) acridine dihydrochloride, upon the growth of seven strains of rapidly growing acid fast bacilli. A 2 mm. loopful of heavy growth from solid media was spread by spatula over the surface of 20 cc.

of 2% glycerine bacto nutrient agar. Dilutions of the drugs were assayed by the cup assay method (Foster, J. W. and Woodruff, H. B., *J. Bact.* 47: 43, 1944). The maximum zone diameter usually appeared by the seventy-second hour of incubation at 36° C. *M. berolinensis*, *M. phlei*, *M. smegmatis*, *M. chelonei*, *M. avium*, *M. leprae* were inhibited in highest dilution by atabrine at 1:40,000 and *M. tuberculosis* at 1:80,000. Both derivatives inhibited all the strains at 1:80,000. Subcultures made from the margin of the cup at the 48 hour period from the atabrine plates were sterile. Stained smears showed attenuated forms with some loss of acid fastness at this time. A search of the literature failed to reveal any previous report of the inhibitory effect of these compounds upon members of the genus *Mycobacterium*. *In vivo* studies are in progress.

**Studies in the rate of dissipation of digoxin in man.** ROBERT C. BATTERMAN and ARTHUR C. DEGRAFF. *Dept. of Therapeutics, New York Univ. College of Medicine.* Studies on the dissipation of digoxin were performed on 38 hospitalized and 12 ambulatory patients. Hospitalized patients were digitalized to minor toxicity by 0.5 to 1.0 mm. of digoxin every 6 hours. At varying intervals thereafter groups of patients were given digoxin according to the same dosage schedule until toxicity recurred. The average patient after a lapse of 24 hours from the last dose required 49 per cent of the initial dose to attain the same effect. After 48 hours the average patient tolerated 84 per cent of the initial dose and after 72 hours, 87 per cent. The rapidity of dissipation was clearly demonstrated in ambulatory patients. After determining the dose of digoxin which, when administered as a daily single dose, resulted in minor toxicity, the patient continued the same total daily dose but in divided amounts. In all of the 11 patients so treated toxicity subsided promptly within a few days or before the next clinic visit. In two of these patients the divided dose was also insufficient for maintenance, since they developed increasing signs of congestive heart failure. In five other trials where the minimal maintenance dose was determined, dividing the dose resulted in an increase in congestive heart failure. Restoration of the undivided dose resulted in recurrence of satisfactory maintenance or development of toxicity.

**Methyl cellulose: its laxative action and effects of chronic feeding on growth and reproduction.** ROBERT O. BAUER (introduced by A. J. Lchman). *Wayne Univ. College of Medicine, Detroit, Mich.* In young rats the time of passage of food through the gastrointestinal tract was the same in the animals fed methyl cellulose as in the controls. With advancing age, the passage time in the methyl cellulose fed rats was greater than in the controls. Two dogs which were fed 2 to 100 grams of this compound

daily for one month showed no significant increase in the weight of the stools for the different levels of intake. The increase was almost exactly that of the dry weight of the agent administered. In man 2.5 to 5.25 grams of methyl cellulose taken orally as gels in 250 c.c. of water had a tendency to be mildly obstipating.

Rats fed 5 per cent of methyl cellulose in a basal diet through three generations showed a definitely greater average increase in body weight than did the controls. Reproductive functions were not impaired. Paired feeding experiments in which 50 per cent of the food intake consisted of the compound, indicated that some loss of weight occurred. This effect could be ascribed entirely to the inability of the rats to ingest sufficient quantities of the diet to maintain normal development.

Formic acid was determined in the urines of the dogs and paired rats. Only minute quantities were found which were within the normal variations of the method employed.

It is concluded that methyl cellulose is non-toxic per os, but is a poor substitute for the accepted colloidal laxatives. Methanol is probably not formed as a degradation product after oral ingestion of methyl cellulose.

**The effect of DDT (2,2-bis(p-chlorophenyl) 1,1,1-trichloroethane) on Protozoa.** MORRIS BELKIN (introduced by R. P. Walton). *Dept. of Pharmacology, Medical College of South Carolina.* Paramecium aurelia, Ameba proteus and Ameba dubia were placed in aqueous suspensions of DDT of varying concentrations ranging from 1-16,000 to 1-256,000. The survival time of the paramecia was about 45 minutes in 1-16,000 and 2 hours in 1-256,000 concentration. An equal degree of sensitivity was exhibited by a rotifer, Hydatina senta. Both species of amebas, on the other hand, immersed in similar suspensions survived for 24-48 hours or longer, depending on the concentration.

Ameba dubia, micro-injected with 5% DDT dissolved in olive oil survived for about 50 hours before lysing. In another series, in which the same species was micro-injected with 15% DDT in olive oil the survival time was almost as long. The digestion of the oil appeared markedly retarded.

Specimens of A. dubia were also "capped" with 5% DDT in liquid petrolatum. The "capping" procedure, carried out with the Chambers micromanipulator, attaches a quantity of oil to the cell membrane of the organism to which it adheres. In contrast with the injected amebas "capped" amebas died in 2 hours. The specific vulnerability of the cell membrane is indicated.

The relatively marked sensitivity of the paramecium and of the rotifer might possibly be attributed to action of DDT on a primitive nervous system.

**The electrical activity of sympathomimetic**

amines at the phase boundary between fats and saline. R. BEUTNER and T. C. BARNES. *Dept. of Physiology and Pharmacology, Hahnemann Medical College and Hospital of Philadelphia.* We have reported previously (Proc. Soc. Exper. Biol. and Med. to be published) that acetylcholine produces negative phase boundary potentials between oils and salines. These experiments were intended to explain the electrical activity of cholinergic nerves. Further experiments of this kind were done with sympathomimetic amines. Although these drugs have an action antagonistic to that of acetylcholine they likewise shift the phase boundary potential to the negative side. But there is a difference in chemical character of the lipid (or oil) upon which the sympathetic, or the parasympathetic drugs, act. Epinephrine is difficult to use in these experiments due to its chemical instability. A more stable amine, paredrine (at 0.05%) shifts the potential difference to the negative side when in contact with benzyl alcohol (pure) to the extent of 4 millivolts, tricaprolin to the extent of 26 millivolts, triacetin plus tributyrin (50:50) to 33 millivolts. (These were selected as representative of glycerides because they possess some conductivity while the higher glycerides are completely insulating electrically.)

In all these cases acetylcholine has no electric effect; this substance works only when in contact with cholesterol or lecithin (each of these to be dissolved in benzyl alcohol) according to the experimental experience so far available. It seems that sympathomimetic amines operate also on glycerides, where acetylcholine fails.

From these findings the difference in action of cholinergic and adrenergic fibers might be interpreted as the result of their chemical composition: the former consisting chiefly of cholesterol and lecithin, the latter of glyceride fats, although they may also contain cholesterol and lecithin.

The cholinesterase of human erythrocytes. RALPH W. BRAUER and MARY A. Root (introduced by Otto Krayer). *Dept. of Pharmacology, Harvard Medical School, Boston.* The location of cholinesterase in the giant axon of the squid has been studied previously and it has been reported<sup>1</sup> that the enzyme is concentrated in the surface layers rather than in the axoplasm. Similar studies have not, so far, been presented for any mammalian tissues. The present work was performed mostly on human erythrocytes. Mendel and co-workers<sup>2</sup> have reported finding a cholinesterase in these cells which will hydrolyze acetylcholine at low concent-

rations, and which readily hydrolyzes acetyl- $\beta$ -methyl choline, but not benzoyl choline. The location of the enzyme within the erythrocyte has been established by the following experiments:

1. Simple hemolysis either by hypotonic saline, or by freezing—thawing in isotonic saline does not change the cholinesterase activity of human and dog erythrocyts.
2. From the dilute hemolysate, 90–100% of the enzyme activity can be recovered in the stroma fraction obtained by centrifuging for 15 minutes at 4000 r.p.m. at pH 5.5.
3. The hemolysate from which the stromata have been removed by filtration through a Seitz filter under N<sub>2</sub> pressure does not show any cholinesterase activity.

On the basis of these findings, it can be concluded that the cholinesterase activity in human erythrocytes is attached to the "stroma" fraction.

Experiments have also been carried out to test the firmness of the attachment of the enzyme to the stromata. It has been found that even if these are mechanically disrupted by passing the dilute hemolysates repeatedly through a Sharples Supercentrifuge, most of the cholinesterase activity can be recovered in the precipitate, i.e., the stroma fragments. Repeated washing of stromata with MM/45 phosphate buffer at pH 5.5 has been found to result in a marked increase in the cholinesterase activity of the cell remnants both total and per cell.

Antibiotic substances active against *M. tuberculosis*. MILTON T. BUSH and (by invitation) H. L. DICKISON, CHARLOTTE B. WARD and ROY C. AVERY. *Dept. of Pharmacology and Pathology, Vanderbilt School of Medicine, Nashville, Tenn.* A strain of mold isolated by one of us (R.C.A.) and identified as a strain of *Aspergillus flavus* Link was found to produce on certain media (2% lactose + 2% Difco Peptone) a culture fluid which inhibited *M. tuberculosis* *in vitro*. By extraction of this fluid we have obtained crystalline impure material which is active against many acid-fast organisms (including the avian, human and bovine types of *M. tuberculosis*), *E. coli* and *S. aureus*. In this mixture there are present at least two weak acids, apparently having very similar physical and chemical properties and showing about the same antibiotic spectrum. We have isolated one pure compound which resembles aspergillic acid except that it has m.p. 96.5–97.5° C corr. It crystallizes from absolute methanol in massive yellow prisms. Microelectrometric titration with NaOH solution gives a neutralization equivalent 230 and an apparent ionization constant (pK') 5.5. The antibiotic activity is 75–100 dilution units per milligram against *S. aureus* and *E. coli*; against *M. tuberculosis* (a quick growing human strain) a concentration of 0.2 mg./cc. produces clear circles of 20 mm. diameter by the agar-plate-cup method. (The inoculum is

<sup>1</sup> a. Boell, E. J., and D. Nachmansohn. *Science*, 92: 513–14, 1940. b. Nachmansohn, D. and B. Meyerhof. *J. Neurophysiol.*, 4: 348–61, 1941.

<sup>2</sup> a. Mendel, B. and H. Rudney. *Biochem. J.*, 37: 59–63, 1943. b. Mendel, B., D. B. Mundel and H. Rudney. *Biochem. J.*, 37: 473–476, 1943.

spread thinly almost uniformly on nutrient agar with a spatula. This method is suitable for assays against quick growing acid-fast organisms and can give results reproducible to  $\pm 15\%$ .

A second crystalline material having m.p. 118-121° C corr. has been obtained. This seems to have the same neutralization equivalent, pK', and antibiotic activity as the pure fraction of m.p. 96.5-97.5°.

We shall soon undertake experiments to ascertain what activity these substances may have *in vivo*.

**A new adrenolytic agent, 2-benzyl-imidazoline (Priseol).** DOROTHY CHESS (by invitation) and FREDERICK F. YONKMAN. *Dcpt. of Pharmacology, Research Division, Ciba Pharmaceutical Products, Inc., Summit, N. J.* This compound has been purported to possess adrenolytic and sympatholytic properties in certain experimental situations (Meier, R. and Meyer, R. Th., Schweiz. med. Wschr. 71: 1206, 1941). We thus chose to study it with our standard technique previously described, (Federation Proceedings 3: 88, 1944) in which salivation, retraction of the nictitating membrane, pupillary changes and blood pressure, all functions affected by sympathetic influences, were studied in urethanized cats.

1. Priscol, 15 to 20 mgm., had no effect on salivation or the pupil.
2. Priscol, 1 mgm., produced a marked, sudden retraction of the nictitating membrane and an acute hypotension enduring for approximately 30 minutes.
3. Priscol, 15 to 20 mgm., produced a marked and sudden lowering of blood pressure (up to 50 per cent) which endured for a period of three hours or more during which pulse and respiration seemed unaffected.
4. The effect of epinephrine, 10 gamma, was reversed from the usual hypertensive to a hypotensive phase. This effect prevailed after 15 to 20 mgm. of Priseol for approximately 3 hours, after which a gradual return to normal epinephrine responses ensued. During recovery biphasic reactions prevailed in which initial hypertension was followed by hypotension. With each successive dose of epinephrine the hypertensive phase became more prominent while the hypotensive phase became less marked with return to normotensive levels.
5. Salivation and pupillary responses to epinephrine were not affected by priscol, 15 mgm.

Thus, although priscol, 15 mgm., was adrenolytic in relation to blood pressure, it was not adrenolytic or sympatholytic in respect to the cervical sympathetic functions studied. The effects of larger doses are now being investigated.

#### Comparative study of the effect of gastric anta-

cids on gastric secretions. BYRON B. CLARK, W. LLOYD ADAMS and JOHN J. ROMANO (by invitation). *Dcpt. of Physiology and Pharmacology, Albany Medical College, Union Univ., Albany, N. Y.* The comparative effect of 5 antacids on the amounts of gastric secretion and hydrochloric acid produced in response to a daily test meal (8 A.M.) has been determined on two Cope pouch dogs, employing the technique previously described (Am. J. Physiol. 139: 356, 1943). The antacids administered three times daily (9 and 11 A.M. and 2 P. M.) were sodium bicarbonate (II), 50 cc. of 2 or 4%; aluminum hydroxide gel (III), 50 cc. diluted 1-4, (Am. J. Physiol., 141: 255, 1944); calcium carbonate (IV), 0.6 gm.; magnesium oxide (V), 0.25 gm.; and sodium citrate (VI), 1 or 2 gm. (I) is the control series. The average percentage changes in hydrochloric acid during the four daily collection periods are shown in the table.

	No. ex.	8-11	11-2	2-5	Day	Night	24 hrs.
I	14	-5	+4	+5	0	+3	+1
II	10	+12	+49	+48	+38	-20	+29
III*	10	-3	-2	+33	+26	+11	+25
IV	10	+12	+26	+30	+19	-9	+15
V	14	+7	+18	+32	+13	-8	+7
VI	12	+2	+10	-5	+2	-16	+2

\* Increases due mainly to one experiment.

Sodium bicarbonate and calcium carbonate produced the greatest and most consistent increases. Magnesium oxide showed increases in only one animal. (See reference for aluminum hydroxide). In general none of the antacids produced a significant decrease in secretion during the 9 hour period following the test meal.

**Some observations on the mechanism of hemolytic anemias produced by drugs.** BYRON B. CLARK, ROBERT W. MORRISSEY (by invitation) and DOROTHY B. BLAIR (by invitation). *Dept. of Physiology and Pharmacology, Albany Medical College, Union Univ., Albany, N. Y.* Observations have been made to determine if intracorporeal methemoglobin alters the resistance of erythrocytes to a number of lysins. The methemoglobinemia was produced *in vitro* by the addition of sodium nitrite to erythrocytes which were subsequently washed three times with saline; standard suspensions of the methemoglobin and normal cells were prepared. Time dilution curves with saponin revealed no difference in behavior of the two types of cells both in the absence and the presence of accelerators (e.g., benzene, quinine, aniline, etc.). Likewise no difference was observed in percentage hemolysis curves with hypotonic saline alone or in the presence of an accelerator (quinine). With sodium glycocholate and taurocholate, little difference was observed at pH 6.2; however, at pH 7.3 the methemoglobin was more resistant to lysis than the normal cells.

moglobin cells were much more resistant, apparently due to a reaction with methemoglobin. Observations on lysolecithin are in progress. Chronic methemoglobinemia maintained in dogs for one month with daily injections of sodium nitrite revealed no evidence of anemia.

The activities of a series of compounds to accelerate saponin hemolysis was determined. Taking the activity of aniline as one, the relative activities were: acetanilid 1.8 (0.8), benzene 3.1, acetophenetidin 3.6, p-aminophenol 7.4,  $\beta$ -phenylhydroxylamine 56, phenylhydrazine 72, and quinine 214. Sulfanilamide, sulfapyridine, sulfathiazole, sulfadiazine, antipyrine and aminopyrine had little activity. Two of the postulated metabolic intermediates of the sulfonamides and aniline derivatives, namely, p-aminophenol and especially  $\beta$ -phenylhydroxylamine, are more active accelerators of hemolysis than the original drugs and may play a part in the production of hemolytic anemias.

**Duration of protective action of barbiturates against picrotoxin.** VERSA V. COLE and H. R. HULPIEU. *Dept. of Biochemistry and Pharmacology, Indiana Univ. School of Medicine, Indianapolis.* Eleven barbiturates have been classified according to the duration of protection against death from picrotoxin: (1) those protecting for one hour or less, (2) those protecting for one hour to two days, (3) those protecting for more than two days. Dosages of nine of these barbiturates were well below the anesthetic level. The barbiturates studied showed different types of curves of protection. The relationship of the individual compounds to each other was quite different from the usual relation based on anesthetic action. The groups of barbiturates were not very different from similar groups classified according to length of anesthetic action.

Male rats weighting from 66 to 80 grams were used. The amount of picrotoxin which killed eight out of ten animals (10 mgm/kgm) was always used as the test dose. The dose for each barbiturate was the minimum amount that would protect at least nine of ten rats from death, when given before the picrotoxin (for short acting barbiturates 20 min., others 1 hr.). A time curve of protection was obtained by giving the picrotoXIN at 40, 60 and 80 minutes after the shortest acting barbiturates, and at 2, 48, 72, 96 and 120 hours after the other barbiturates. This method appears to give some information not obtained by other methods.

**The effect of lithospermum ruderale on the oestrous cycle of mice.** ELIZABETH M. CRANSTON (introduced by Raymond N. Bieter). *Dept. of Pharmacology, Univ. of Minnesota, Minneapolis, and the Division of Plant Exploration and Introduction, United States Dept. of Agriculture.* Fluid-extract of Lithospermum ruderale was administered orally to mice by mixing it in the diet.

Treated adult female mice, with previously regular oestrous cycles, developed prolonged periods of dioestrous. Injections of estrone or gonadotropic hormone administered to mice during treatment induced the development of oestrous. A loss in body weight in the presence of an increased food and water intake occurred. No difference in basal metabolism between treated and control mice was noted.

In female mice, twenty-one days of age, treatment with lithosperm for ten days caused decreases compared with control mice, in body growth of 25 per cent, in ovarian weights of 37 per cent, in weights of uterus plus vagina of 51 per cent, in thymus weights of 62 per cent and in pituitary weights of 40 per cent. In male mice, twenty-one days of age, treatment for ten days caused decreases in body growth of 34 per cent, in weights of testes of 26 per cent, in weights of seminal vesicles plus prostate of 66 per cent, in thymus weights of 67 and in pituitary weights of 45 per cent. Inanition sufficient to cause decrease in body growth comparable with treated mice caused significantly smaller decreases in the weights of uterus plus vagina and seminal vesicles plus prostate.

The results indicate that lithosperm acts directly on the pituitary gland to decrease the formation of gonadotropic hormone.

**Oral penicillin.** WINDSOR C. CUTTING, RICHARD M. HALPERN, ERNEST H. SULTAN and CHARLES A. ARMSTRONG. *Depts. of Pharmacology and Therapeutics, and of Medicine, Stanford Univ. School of Medicine, San Francisco, Calif.* In 9 out of 12 trials in 9 persons with gastric achlorhydria, penicillin was absorbed when given orally producing an average blood concentration at 1 hour of 0.06 u. per cc. Conjoint use of other agents failed to promote the absorption. Eight trials in 5 persons without gastric achlorhydria did not result in demonstrable absorption, even with the addition of alkaline or other protective substances. These results confirm the destructive power of gastric acidity.

In 5 normal persons receiving penicillin enclosed in 4 different enteric coatings, no absorption occurred. However, inclusion of agents which promote absorption resulted in satisfactory blood levels. Although achlorhydric persons apparently absorbed penicillin because it was not destroyed, the best protection which could be devised would not be adequate in normal persons, without adding an agent which could promote absorption.

Therefore, 110 trials were made in 35 persons with penicillin plus an agent to promote absorption, both enclosed in a resinous (Enterab), or plastic (cellulose hydrogen acetate phthalate) enteric coating. The added drugs (30 different agents plus combinations) included antisepsics, surface tension reducers, solvents, salicylates, and protoplasmic poisons. Most effective were methenamine, ethyl

been correlated with blood levels of the drugs, caloric intakes and with pathological changes in the thyroids, kidneys and reproductive organs. Histological and biochemical studies are in progress.

**Chemotherapeutic activity in local infections.** N. ERCOLI, M. N. LEWIS and E. HARKER (introduced by R. H. K. Foster). *Research Laby., Hoffmann-La Roche, Inc., Nutley 10, N. J.* The local antibacterial activity of different chemotherapeutic agents, including antibiotics of microbial origin, was studied in comparison to their systemic activity in generalized infections. The experiments which were carried out with  $\beta$ -hemolytic streptococci, staphylococcus aureus, and C. diphtheriae showed that topical activity and systemic activity are two different functions of the chemotherapeutic agents and have to be determined with different methods.

An appropriate technique for quantitative determination of local activity *in vivo* has been developed; the results obtained with certain triphenylmethane dyestuffs, acridines, quinolines, and sulfonamides, as well as with tyrothricin and penicillin, show that some of these agents are only active by local administration, while in others, the systemic effectiveness towards generalized infections definitely prevails. Penicillin was found to be the only agent which exerts a satisfactory local antibacterial activity and is at the same time, highly effective in generalized infections.

Moreover, the quantitative comparison of the local activity in streptococcal, staphylococcal, and diphtherial infections showed a certain degree of specific activity of the different agents towards the test micro-organisms.

**Vitamin K activity of some sulfonamide derivatives of menadione and related agents.** P. L. EWING, CHAUNCEY D. LEAKE, G. A. EMERSON and (by invitation) EDITH JU-HWA CHU. *Dept. of Pharmacology, Univ. of Texas Medical Branch, Galveston, and Biochemical Inst., Univ. of Texas, Austin.* The vitamin K activity of ten compounds was estimated by their effects on clotting and prothrombin time after intramuscular injections in 0.01 M/Kg doses as aqueous and oily suspensions or solutions into vitamin K deficient White Leghorn chicks. The compounds tested included the parent substance, 4-azo-sulfanilamide- $\alpha$ -naphthol ( $C_{10}H_8OH.N.C_6H_4.SO_2NH_2$ ) and its 2-methyl, 2-ethyl, 2-phenethyl, 2-propyl, 2-butyl, 2-amyl, 2-carboxy, 2-carboxy-N<sub>1</sub>-acetyl, and 1-amino-2-methyl derivatives. The synthesis of these agents was instigated and carried out by Dr. Edith Ju-Hwa Chu. The two 2-methyl derivatives were the only ones exhibiting vitamin K activity, the 2-methyl- $\alpha$ -naphthol derivative showing initial effects approximately equal to menadione but less prolonged, whereas the 1-amino-2-methyl-naphthalene derivative required about 5 days to reach its maxi-

mum effect of about 50% that of menadione. Deviation from the menadione structure appears to detract definitely from the vitamin K activity of the compounds although the diazo union with sulfanilamide does not interfere appreciably, except perhaps through decreased solubility.

**Studies on the general pharmacology of dibutoline.** R. M. FEATHERSTONE and N. G. WHITE (introduced by E. G. Gross). *Dept. of Pharmacology, College of Medicine, State Univ. of Iowa, Iowa City.* Dibutoline, one of a series of recently synthesized surface-active choline derivatives, was studied to determine its toxicity, its effectiveness as an antispasmodic agent, and its probable mode of action. The LD<sub>50</sub> in rats was found to be 22 mgm/kgm. for intraperitoneal injection, but the compound had no adverse effects when given orally in concentrations twenty times as great. Dibutoline, in a similar manner to atropine, was more effective in preventing or overcoming the stimulation in isolated intestinal muscle strips induced by neurotropic drugs like mecholyl than that induced by musculo-stimulant drugs like barium chloride. In unanesthetized dogs which had been prepared with Thiry-Vella loops, gastrotomies, and colon fistulae, dibutoline injected subcutaneously was equally effective with atropine in relaxing the stomach, small intestine, and colon, and in blocking the action of prostigmine on these structures. Administrations of large doses orally were likewise effective. The fall of blood pressure following injection of acetylcholine in an anesthetized dog was prevented by dibutoline as it was by atropine. Although dibutoline injected subcutaneously to unanesthetized dogs had no marked effect on the tonicity or capacity of the urinary bladder, the drug acted in a manner similar to atropine in overcoming the reactions following parasympathetic stimulation of this organ. When the effect of dibutoline on salivary secretion was studied, evidence was obtained that dibutoline, like atropine, acts to block only the cholinergic nervous system. Studies on the pulse, uterine, and bronchodilating effects of dibutoline were also carried out.

**The pain threshold raising action of a number of new phthalidyl derivatives.** EDWIN J. FELLOWS. *Temple Univ. School of Medicine.* The pain-threshold raising action of 1-phthalidyl-1-aminopropane HCl in rats and cats suggested the desirability of examining other modifications of the phthalidyl nucleus for analgesic activity. The following new compounds therefore have been tested in the form of hydrochlorides in cats for pain-threshold raising action: 1-amino-2-phthalidylethane(I); 4, 5, 6-Trihydroxyphthalidylidimethylaminomethane(II); 1-amino-1-phthalidyl-n-butane(III); 1-Dimethylamino-1-phthalidylpropane(V); N-Ethyl-1-phthalidyl-1-aminopropane(VI); 1-amino-1-phthalidyl-

*n*-pentane(VII); 1-amino-1-Phthalidyl-*n*-Hexane (VIII); *n*-Benzyl-1-amino-1 phthalidyl propane (IX); N-Benzyl-phthalidylmethylethylamine(XI). Over a non-toxic dose range II, VI, X and XI were devoid of pain threshold-raising activity. Compounds I, III, V, VII, VIII and IX evidenced pain threshold raising activity only in a dose range slightly below a toxic level. All of the present derivatives therefore appear less interesting than 1-Phthalidyl-1 aminopropane.

The effect of the hydrochlorides of phthalidyl-aminomethane (I), 1-phthalidyl-1-aminopropane (III), on pain threshold. EDWIN J. FELLOWS and RAYMOND W. CUNNINGHAM. Temple Univ. School of Medicine In non-toxic doses in rats (D'Amour-Smith Method) and in cats (Eddy Method) derivatives II and III evidenced pain-threshold raising activity but I was devoid of this action. Compound III appeared to be the more interesting of the two active agents. Analgesic activity was detectable in rats following doses of from 100-300 mgm/kgm of III intraperitoneally. In cats, III evidenced a prolonged and intense pain-threshold raising action after intraperitoneal injection of 75-250 mgm/kgm. The LD<sub>50</sub> of III in rats was 600 mgm per kgm intraperitoneally and 2.0 grams per kgm per os. Because of its intensity and long duration of analgesic action as well as its low toxicity compound III appears worthy of an extensive pharmacological investigation.

Cumulative effects of the prolonged administration of quinaecline (atabrine). O. GARTH FITZHUGH and ARTHUR A. NELSON (by invitation). Division of Pharmacology, Food and Drug Administration, Federal Security Agency, Washington, D. C. When quinaecline is administered to rats in the diet for two years, symptoms are produced by concentrations of 100 p.p.m. or more. At the 100 p.p.m. level the symptoms are slight, at higher levels the symptoms become progressively more severe. Grossly in the rats on the higher dosages of quinaecline the liver shows severe necrosis and varying degrees of hyperplasia; there are also present generalized yellow staining of the viscera, peritoneal adhesions, relative enlargement of the spleen and atrophy of the testis. Microscopically the outstanding changes are necrosis of the liver, focal necrosis of the myo-cardium and of voluntary muscles, hypertrophy and rarefaction of the cardiac muscle fibers and hyperplasia of the bone marrow. The important hematologic change is a marked leukocytosis in the rats on the higher concentrations of quinaecline. Quinaecline appears to cause a cumulative effect on the heart, so that a low dosage level over a long time can lead to a high grade of damage. Damage to the liver at the dosage levels studied has less of a

In terms of body weight of the rat 40 mg. or more of quinaecline per kg. per day produced death within a short time. A dosage of 10 mg. per kg. of body weight per day increased the mortality rate and frequently caused visceral changes. Our lowest dosage of about 5 mg. per kg. per day rarely caused any visceral change. This dosage is several times the human dosage in the prophylactic treatment of malaria.

Cumulative distribution curve of digitalis action in man by oral administration. HARRY GOLD, WALTER MODELL and HAROLD OTTO (with the technical assistance of JENNY OPPENHEIM). Dept. of Pharmacology, Cornell Univ. Medical College, New York, N. Y. While there are several studies on the range of sensitivity of animals to digitalis, there are no satisfactory data bearing on this point in man. We prepared a cumulative distribution curve for man with the U.S.P. Reference Digitalis T-wave change in the electrocardiogram in 86 patients with regular sinus rhythm. A control tracing was taken, an oral dose was given, and the effect was determined in a tracing taken about 24 hours later. A month elapsed for the elimination of the drug, and the above was repeated. This was continued until a pair of doses was found 22 to 25 percent apart, one causing no effect and the other lowering the T-wave. The threshold dose was taken as the smallest dose causing a lower T-wave than the lowest of the controls when examined as unknowns. All doses below the negative were assumed to be ineffectual and all doses above the first positive were assumed to be effectual. The treatment of the data in this way supplied 833 units for the computation of the curve. The curve has the typical sigmoid form described in the case of digitalis for frogs and cats. It shows that by oral administration in man, the range of variation in sensitivity to digitalis is about 300 percent. A dose  $\pm 25$  percent of the mean includes about 70 percent and  $\pm 50$  percent includes about 95 percent of the population. The curve lends validity to the single dose method of digitalization and supplies a standard which may be put to use in the human method of assay of digitalis.

The anticonvulsant properties of dimethyl-N-methyl barbituric acid and 3,5,5-trimethylhexazolidine-2,4-dione (tridione)<sup>1</sup>. LOUIS GOODMAN and CORINNE MANUEL (by invitation). Dept. of Pharmacology, Univ. of Utah School of Medicine, Salt Lake City. Dimethyl-N-methyl barbituric acid and tridione were examined as anticonvulsants against metrazol in mice, rats, rabbits, cats and monkeys, and against electroshock using standard electroshock cycle stimulation, and Spiegel.

<sup>1</sup> Aided by a grant from the Ab.

in rabbits, cats, and monkeys. Implanted epidural electrodes were also used in rabbits. The anticonvulsants were administered i.p. or i.v.; the metrazol, s.c. or i.v. Experimental and control groups of mice and rats were considered as samples of a normal population; rabbits, cats and monkeys were individually standardized to metrazol and electroshock convulsion over a period of weeks, and the final criterion for the occurrence of a convulsion was the cortical seizure pattern recordable electroencephalographically.

In doses practically devoid of c.n.s. depressant effects, dimethyl-N-methyl barbituric acid (100-125 mgm/kg, i.p.) and tridione (500 mgm/kg, i.p.) proved to be effective anticonvulsants against metrazol in all species tested, affording complete protection against one to two times the standard convulsant dose of metrazol ( $CD_{25+}$ ). Residual anticonvulsant action from single doses could be noted up to 48 hours. Dimethyl-N-methyl barbituric acid, however, did not afford appreciable protection against electroshock, either in raising the electrical threshold or in modifying the severity or duration of seizures. In contrast, tridione exerted definite protective action against electroshock convulsions in that seizures were considerably shorter in duration and less severe. Like the barbiturate, however, tridione had little effect on the electrical threshold for production of convulsions. The significance of differences between anticonvulsants in protection against electroshock seizures and metrazol convulsions is under investigation.

Experimental indices for comparing the efficacy of compounds with anticonvulsant and antiepileptic properties. LOUIS GOODMAN and JAMES E. P. TOMAN (by invitation). *Dept. of Pharmacology and Physiology, Univ. of Utah School of Medicine, Salt Lake City.* A systematic comparative study is being conducted of anticonvulsants and antiepileptics with respect to mechanisms of action, protection against metrazol-induced seizures, alteration of threshold for or decrease in severity and duration of electroshock convulsions, effect on duration of electroconvulsions produced by supramaximal currents, effect on cortical discharges produced by single cortical shocks, and influence on the normal EEG. Among agents being investigated are phenobarbital, diphenylhydantoin, 3,5,5-trimethyloxazolidine-2,4-dione (tridione), and benzimidazole. (Techniques and animal species employed are described in abstracts by the authors in these Proceedings.) Doses selected were those least depressant to the c.n.s. and yet exhibiting definite protective action in one or more categories. A major purpose in these studies is to elucidate similarities and differences in mechanisms of drug action which may explain the known therapeutic specificity of antiepileptic agents. Data obtained to date permit

the following comparative scoring of compounds with respect to certain of the above named indices:

Indices	Pheno-barbital	Dilantin	Benzimi-dazole	Tridione
Protection against metra-zol seizures.....	++	0	+	+++
Increase in threshold for electro convulsion.....	++	+?	+++	+?
Decrease in severity of threshold electrocon-vulsion.....	+++	+	+++	++
Decrease in duration of maximal electrocon-vulsion.....	+++	+++	+	++
Increase in threshold for cortical secondary dis-charge.....	0	0	+	0

+++ = excellent, ++ = good, + = fair, 0 = inactive.

[These investigations have been made with the assistance of grants from the Committee on Therapeutic Research, Council on Pharmacy and Chemistry, American Medical Association, and from the Abbott Laboratories.]

The antibacterial properties of dicumarol. ANDRES GOTTH (introduced by Donald Slaughter). *Dept. of Physiology and Pharmacology, Southwestern Medical College, Dallas, Texas.* Dicumarol was found to possess marked antibacterial properties. Organisms inhibited when dicumarol was present in broth in the concentration of 1:100,000 were *Staphylococcus aureus*, *Streptococcus pyogenes*, *Streptococcus viridans*, and *Bacillus anthracis*. Organisms inhibited by a concentration of 1:25,000 were *Corynebacterium diphtheriae*, *Brucella abortus* and a fast-growing, non-virulent human strain of *Mycobacterium tuberculosis*. Organisms not inhibited when the concentration of dicumarol was as high as 1:25,000 were *Streptococcus fecalis*, *Bacillus subtilis*, *Clostridium Welchii*, *Eberthella typhosa*, *Salmonella paratyphi A*, *Escherichia coli*, *Proteus vulgaris*, and *Pseudomonas pyocyanea*.

The mode of antibacterial activity was essentially bacteriostatic and the growth inhibition caused by dicumarol was not antagonized by various naphthoquinones.

The effect of sympathomimetic amines on the synthesis of cocarboxylase in vitro. WM. M. GOVIER, VERA BERGMANN (by invitation) and KARL H. BEYER. *Dept. of Pharmacology, The Medical-Research Division, Sharp and Dohme, Inc., Glenolden, Pa.* The effect of six sympathomimetic amines (phenethylamine, N-methyl phenethylamine, N-dimethyl-β methyl phenethylamine, amphetamine, tyramine, and β(p-hydroxy-phenyl) isopropylamine on the synthesis of cocarboxylase by normal pigeon liver slices from thiamine and pyrophosphate has been investigated. Cocarboxylase was estimated manometrically after

incubation of slices, substrates, and drugs for one hour in an atmosphere of oxygen at 37°. All of these compounds have been found to produce an increase in cocarboxylase synthesis by this tissue but no correlation has been demonstrated between the structure of the amine and the amount of cocarboxylase synthesis observed.

Preliminary observations have appeared to indicate that the increase in cocarboxylase is due to an increase in phosphorylation rate during the first few minutes of incubation since phosphorylation of thiamine proceeds only to the point of saturation of carboxylase apoenzyme with cocarboxylase.

The investigation is being extended to include other phenethylamine derivatives and further experimentation is in progress to elucidate the mechanisms involved.

A solubilized form of phenolphthalein. M. G. GRAY (introduced by Walter L. Mendenhall). *Arthur D. Little, Inc. Chemists, Cambridge, Mass.* The preparation and properties of phenolphthalein betadiglucoside are described. Its solubility characteristics permit the preparation of a low alcohol elixir, suitable for use on pediatric practice and capable of being dispensed in fractional doses. Its laxative action is approximately twice that of phenolphthalein U.S.P. XI and it differs from the glucosides as a class in that it does not have the characteristic bitter taste.

Clinical tests have been made with groups of subjects from infancy to old age and these show that its usefulness is superior to phenolphthalein. The diglucoside form caused no allergic response in 223 subjects ranging from 1½ to 86 years of age. The intended dosage is between ½ and 3 grains. Extensive toxicity tests indicate that 0.5 gram can be safely tolerated by man.

The oxygen content of venous blood in traumatic shock. RAYMOND GREGORY (by invitation) and PAUL L. EWING. *Depts. of Internal Medicine and Pharmacology, Medical School, Galveston.* Studies of continuous arterial blood pressures, hematocrits, specific gravity of plasma, arterial and venous blood oxygen content were made on eleven dogs traumatized quantitatively by the application of a definite number of blows per kilo of a padded "hammer" weighing 2.3 K and allowed to fall from a measured height.

The inadequacy of blood pressures and hematocrit studies as criteria of impending shock is attested to by the abrupt death of animals two to thirteen hours after trauma with persistently normal hematocrit values, and mean systolic blood pressures of 100 mm. Hg or more. The oxygen content of venous bloods drawn at two to four hour intervals following trauma showed progressive and great decrease in all animals that died, failed to show a decrease in animals that survived. Extreme decrease in oxygen content of venous blood may occur

many hours before hematocrit or blood pressure changes or before abrupt death.

Properties of enzyme inhibitors extracted from liver. MARGARET E. GREIG and WILLIAM E. DE TURK (introduced by Paul D. Lamson). *Vanderbilt Univ. School of Medicine, Nashville, Tenn.* In investigating the causes of metabolic changes in shock we found that when excised liver was made anoxic its ability to oxidize lactic and *d*- and *l*-amino acids was markedly decreased. The addition of a water extract of ground liver to whole tissue or to the isolated enzymes, lactic dehydrogenase or *d*-amino acid oxidase, also produced a similar decrease in ability to metabolize these substrates. Isolated carboxylase (yeast or animal) was unaffected by the liver extract.

The active principle or principles are thermolabile and non-dialyzable. They appear to be globulins and are precipitated by half saturation with  $(\text{NH}_4)_2\text{SO}_4$  or by full saturation with  $\text{MgSO}_4$  or  $\text{NaCl}$ .

The factor inhibiting *d*-amino acid oxidase seems to be separable from that inhibiting lactic dehydrogenase since purification procedures involving precipitation with  $(\text{NH}_4)_2\text{SO}_4$ , adsorption upon  $\text{Cu}(\text{OH})_2$  and subsequent elution yield preparations which are uniformly active against *d*-amino acid oxidase, but activity against lactic acid dehydrogenase is sometimes lacking.

Inhibitions of *d*-amino acid oxidase activity of 35% have been produced by amounts of factor equivalent to 0.05 mg. N in 2 cc. The factor produces its inhibition by its action on the apoenzyme.

The inhibitory effect is greatest around pH 6. Phosphate concentrations above 0.03 M inhibit its activity.

The inhibition appears to be reversible since by increasing the pH of the medium in which the liver factor is allowed to act on *d*-amino acid oxidase, the percentage of inhibition produced by the factor is reduced.

Experiments are underway to determine the effect *in vivo* of these extracts injected intravenously.

An investigation on the development of tolerance to barbiturates in experimental animals. CHARLES M. GRUBER and GOLDIE FREEDMAN (by invitation). *Dept. of Pharmacology, Jefferson Medical College, Philadelphia.* This work, undertaken to determine whether or not experimental animals develop a tolerance to barbiturates, was done on dogs, rabbits and rats. The dogs were given butisol sodium intravenously every other day. The rabbits were studied in batches of 7 to 20. Some of them were given intravenously amytal sodium, others butisol sodium or cyclopentone every other day. Pentobarbital sodium or seconal sodium were administered to some every day and others received evipal sodium twice each day. The rats

were also divided into lots of 10 to 18 each. Some of these were given butisol sodium intraperitoneally every other day, others pentobarbital sodium, cyclopal, oral sodium or seconal sodium.

The duration of the hypnosis produced by these drugs was the basis from which conclusions were reached as to the production of tolerance. Some experiments were performed in which after the rabbits showed a definite decrease in the period of sleep produced by a barbiturate the LD<sub>50</sub> of that drug was given intravenously. Experiments were also performed to determine if an animal tolerant to one barbiturate was also tolerant to others.

In the 14 dogs used the third injection of butisol sodium was followed by a decrease of 42 per cent in the duration of the induced sleep. After the third injection the average duration of hypnosis was shortened by 47 per cent in 81 rabbits with butisol sodium, by 36 per cent in 58 animals with amytal sodium, by 47 per cent in 71 animals with pentobarbital sodium, by 45 per cent in 56 animals with seconal sodium, by 37 per cent in 12 animals with cyclopal and by 36 per cent in 10 animals with evipal sodium. The average decrease in the period of sleep with butisol sodium in 84 rats was 38 per cent, with pentobarbital sodium in 14 animals 50 per cent, with cyclopal in 18 animals 25 per cent, with oral sodium in 10 animals 19 per cent and with seconal sodium in 12 animals 15 per cent.

All of the rats which showed a decrease in the duration of sleep following repeated injections of butisol sodium showed a similar decrease following pentobarbital sodium and vice versa. All of the rabbits which became tolerant to repeated administrations of butisol sodium showed a similar tolerance to subsequent injections of pentobarbital sodium and visa versa. In the same way a tolerance to amytal sodium is followed by tolerance to pentobarbital sodium and vice versa. Dogs made tolerant to butisol sodium proved to be tolerant to pentobarbital sodium. Although the hypnotic effect becomes less after repeated injections of a barbiturate and cross tolerance can be established never-the-less there was produced no increase in the resistance of our rabbits to the median lethal dose of the drug. In fact the LD<sub>50</sub> of pentobarbital sodium and seconal sodium injected intravenously killed 80 to 86 and 60 to 70 per cent of the animals respectively. From these results it appears that animals become resistant to the hypnotic effect of the barbiturate but not to its toxic actions.

A liquid medium for the evaluation in vitro of proposed amebacides.<sup>1</sup> EDER LINDSAY HANSEN (introduced by Gordon A. Alles). Division of Phar-

macology and Experimental Therapeutics, Univ. of California Medical School, San Francisco. Laidlaw et al. in 1926 and 1928 (Parasitology 18: 206; 20: 207) reported that emetine was adsorbed by solid egg in Locke-egg-serum medium and that, in a medium containing only serum and saline, its amebacidal activity was 100 times greater. In this liquid medium, however, *E. histolytica* isolated with bacterium 't' by Dr. C. W. Rees (National Institute of Health) could not be maintained.

A satisfactory egg infusion medium was prepared by autoclaving for 55 minutes at 125°C., 150 cc. of Stone's-Locke's solution (Am. J. Trop. Med. 15: 681, 1935) to which the chopped coagulum from a beaten whole egg had been added. The liquid was filtered with the aid of Hy-flow Supercel, the volume restored to 150 cc., and 0.5% of Wilson's liver extract added. Culture tubes were made with 4.5 cc. of liquid, sterilized by 10 minutes autoclaving, sterile starch added, and 0.5 cc. of ameba culture used for the inoculum. The initial pH was about 8.3. After 48 hours at 37°C. the pH ranged between 7.4 and 6.3.

The ameba could be maintained for at least three transfers from egg slope medium. Second transfers were used for the tests of amebacides. Since no solid adsorbing material was present the amebacides were effective in greater dilutions than in the egg slope medium.

The medium described by Balainuth and Sandza (Proc. Soc. Exper. Biol. and Med. 57: 161, 1944) confirmed our experience. The difference in our method is that the filtration and longer heating prevented the tendency for a flocculum to form during sterilization.

Continued administration of phenobarbital and diphenylhydantoin. P. J. HANZLIK. Dept. of Pharmacology and Therapeutics, Stanford Univ. School of Medicine, San Francisco, Calif. Continued administration of phenobarbital sodium and diphenylhydantoin sodium in low (0.01 per cent) and high (0.1 per cent) concentrations in the diet to white rats for months showed that phenobarbital is more injurious. This was supported by the following results: greater stunting of growth and decrease in body weight, more frequent nasal bleeding and encrustation of eyelids, greater mortality, and lesser voluntary running activity with phenobarbital. Ataxia was not evident, and an increase in threshold of cortical excitability was questionable. The decrease in body weight and running activity of phenobarbital were partly reversed when the animals were switched to normal diet. Feeding and injecting sodium succinate, an alleged antidote for tissue effects of barbiturates, did not prevent the actions of phenobarbital; in fact, there was evidence of liver injury. Other possible antagonists are being tested. The condition of animals on diphenylhydantoin was often as good as

<sup>1</sup> The work described in this paper was done under a contract, recommended by the Committee on Medical Research, between the Office of Scientific Research and Development and the University of California.

that of unmedicated controls. The difference between these two drugs, given for long periods, agrees, in general, with the known difference when they are given in therapeutic or acute toxic doses.

The ratio of the concentration of alcohol in heart blood and in blood from peripheral veins. R. N. HARGER, H. R. HULMEU and VERSA V. COLE, Indiana Univ. Alcohol was administered by stomach tube to 17 dogs in doses of 1 to 4 grains per kilo. At intervals blood samples were drawn simultaneously from the heart and the saphenous vein and analyzed for alcohol content. The Saphenous/Heart blood alcohol ratios found for the various time intervals employed were: 15 min., 0.67 to 0.96; ave. 0.83; 30 min., 0.79 to 1.02, ave. 0.91; 1 hr., 0.87 to 1.11, ave. 0.99; 2 hrs., 0.97 to 1.10, ave. 1.01; and 3 hrs., 0.88 to 1.04, ave. 0.99.

With 14 of the animals samples of blood were taken from the femoral vein within two minutes after the heart samples. The Femoral/Heart blood alcohol ratios obtained were: 15 min., 0.67 to 0.94, ave. 0.80; and 30 min., 0.80 to 1.09, ave. 0.89.

Contrary to the claim of Haggard and Greenberg (*J. Pharmacol. & Exper. Therap.*, 52: 150, 1934), our results indicate that there is no great lag in the alcohol level in the peripheral venous blood as compared with arterial blood. For time intervals longer than 15 minutes, blood from a peripheral vein is about as good as arterial or capillary blood for medicolegal purposes.

Studies on the absorption of pellets of desoxycorticosterone acetate. HARRY W. HAYS (by invitation), E. OPPENHEIMER, DONALD R. MATTHESON (by invitation) and JOSEPH LEIN (by invitation). Dept. of Pharmacology, Ciba Pharmaceutical Products, Inc., Summit, N. J. The absorption curve of cylindrical pellets ( $h = 0.36$  em.,  $r = 0.32$  em., 125 mg.) of Desoxycorticosterone Acetate (DCA) was the same in normal and adrenalectomized dogs. Although it was experimentally established that variation of the pressure (15,000 to 60,000 lbs. per square inch), or size of the crystals (large or small), used in making pellets did not influence the absorption rate, an assay of pellets seemed advisable in order to guarantee the production of a uniform pellet. By a statistical analysis of almost 300 individual data selected from ten different pellet batches, it was determined that from thirty-four to fifty-one days after implantation, the average daily absorption for a group of four pellets should be 0.40 mg. per day with  $\sigma = \pm 0.046$ . Data obtained between zero to thirty-three days proved to be erratic, due to the steep slope of the curve, while later periods became impractical for an assay method. Nevertheless, using plasma volume determinations in adrenalectomized dogs, we obtained proof that absorption from DCA pellets

began within forty-eight to seventy-two hours after implantation.

Capsule formation was observed in all instances but did not seem to be an essential factor in absorption rate. Definite changes could be accounted for however by "ghost" formation. (Folley '42). Evidence of the "ghosts" formation was found by (1), dissolving the pellet in alcohol; (2), by absorption data obtained after reimplantation; (3), by a mathematical analysis of the absorption of pellets of different sizes.

In close agreement with the experience in Addison patients, we have maintained adrenalectomized dogs two hundred and eighty-seven days with a single group of four pellets before being replaced by new ones.

Pressor effects of 2-naphthyl-1'-methylimidazoline HCl in dogs and cats. HARRY W. HAYS, DONALD R. MATTHESON and DOROTHY R. CHESS (introduced by E. Oppenheimer). Dept. of Pharmacology, Ciba Pharmaceutical Products, Inc., Summit, N. J. Studies have been carried out on the effect of 2 naphthyl-1'-methylimidazoline HCl (Privine) on the blood pressure of dogs and cats, anesthetized with either Dial or Sodium pentobarbital. A total of twenty-five dogs and thirty cats were used in these experiments.

The minimal effective dose of Privine injected intravenously to produce a 10 min. rise in blood pressure was 1-5 micrograms per kilogram for the dog and 5-10 micrograms per kilogram for the cat. Successive injections of 1-5 micrograms per kilogram gave a consistent pressor response in the dog, while doses of 10-40 micrograms per kilogram produced a definite tachyphylaxis after four or five injections, particularly with a dose of 40 micrograms per kilogram. In the cat, successive doses of 10-40 micrograms per kilogram gave consistent pressor response while 100 micrograms per kilogram produced a marked tachyphylaxis. In both of these species cardiac irregularities were produced with these higher doses as well as a Cheynes-Stokes' respiration.

When epinephrine was injected intravenously 1.5 micrograms per kilogram after previously administered cocaine 10 milligrams per kilogram subcutaneously, the usual potentiation of the epinephrine response occurred. However, when privine was given following cocaine no potentiation was observed. Again, privine was unlike epinephrine in that no hypotension developed after previously administered ethyl yohimbine.

As previously stated 40 micrograms per kilogram of privine produced a marked tachyphylaxis after three or four injections. If epinephrine was injected alternately with privine there was a progressive increase in the response to epinephrine as tachyphylaxis developed to privine. This potentiation was sometimes greater than that which was

produced with cocaine, being four to five times greater than the control epinephrine response, but only in dogs.

**Autonomic drug action on isolated segments of mouse intestine.** LLOYD W. HAZLETON and EMILY A. M. GODFREY (by invitation). *The George Washington Univ. School of Pharmacy.* A modification of Sollmann and Rademakers' arrangement for studying intestinal segments, permitting direct recording of activity, has been employed to study certain phases of the action of autonomic drugs. The method permits the use of a control segment in the same bath and the administration of the drug either into the bath or into the lumen of either segment. Mouse intestine has been used thus far.

The objective of the present report is to summarize some of the aspects of the method. After the setup is arranged the dose of acetylcholine which will produce an optimal response is determined. The character of the response following internal or external application is determined by the nature of the drug. For example: acetylcholine or epinephrine placed in the bath results in contraction or relaxation proportional to the size of the dose, while if either drug is placed in the lumen these results are not manifest. If atropine or physostigmine is placed in the bath cessation or exaggeration of activity will result. However, if these drugs are placed in the lumen of one segment the characteristic response will be elicited while the control segment will give normal tracings. Upon washing from the lumen with Loeke-Ringer's solution the characteristic action of any of these drugs is obtained immediately in both segments.

It is interesting to note that these responses are analogous to those following oral or parenteral administration of these drugs to intact animals. Further studies are designed to test the extent of this correlation in other drugs.

**The potentiation of the pressor effects of acetaldehyde and acetaldehyde ammonia by ergotamine.** THEODORE KOPPANYI. *Georgetown Univ., School of Medicine.* In dogs, under nembutal anesthesia, ergotamine tartrate in doses from 0.05 to 1.0 mg./kg. by vein potentiates the pressor effect not only of epinephrine but also of intravenous doses of acetaldehyde (5-10 mg./kg.) and acetaldehyde ammonia (5-10 mg./kg.). This ergotamine potentiation may result in the increase of the pressor effects of acetaldehyde and acetaldehyde ammonia from 4 to 5 times that of the original height and duration. The latent period between the intravenous injection of these pressor drugs and their effect on the blood pressure is appreciably increased by ergotamine. The duration of action of ergotamine is about one hour.

This effect of ergotamine on the pressor effect of acetaldehyde and acetaldehyde ammonia is not

due to epinephrine liberated from the suprarenal glands, for it occurs also in the absence of these structures.

In dogs under ether and urethane anesthesia, ergotamine does not potentiate the pressor effects of acetaldehyde and acetaldehyde ammonia, but frequently causes their reversal.

It was found that ergotamine synergizes with the central depressant actions of ether and nembutal. The anesthetic doses of these latter drugs are appreciably decreased by previous administration of ergotamine.

The theory that ergotamine accelerates the rate of oxidation of epinephrine and other oxidizable pressor drugs is definitely disproved by these experiments. The exact mode of ergotamine action still remains to be determined.

**Studies on barbiturates. XXIX. The delay in onset of action of intravenously injected barbital solutions.** THEODORE KOPPANYI. *Georgetown Univ., School of Medicine.* It is well-known that following intravenous injection of solutions of sodium salts of barbital and phenobarbital there is a marked delay in the onset of action (from 10-20 minutes), whereas salts of other barbituric acids given by vein produce anesthesia almost instantaneously. Klimesch<sup>1</sup> and Klimesch and Starkenstein<sup>2</sup> endeavored to explain this phenomenon by the assumption that the onset depends upon the conversion of the sodium salt to the lipid-soluble acid and that the lag in the onset of anesthesia in the case of barbital and phenobarbital is due to a slow rate of conversion and this parallels the hydrolysis of the salts in vitro. This explanation was questioned by Bush<sup>3</sup> who showed that there was no correlation between the hydrolysis of the sodium salts of various barbiturates, their acid-salt ratios at the pH of the blood, and the rate of onset of anesthesia.

Koppanyi<sup>4</sup> has shown that there is an immediate conversion of sodium barbital to the acid form when added to drawn blood. This writer has recently developed a method by which diethylbarbituric acid can be dissolved in water using propylene glycol as a common solvent. Accordingly, 5 per cent solutions of diethylbarbituric acid in water-propylene glycol mixtures could be injected intravenously. In dogs, following the injection of 200 mg. of barbital per kg. the onset of ataxia and prostration was delayed for an average period of 15 minutes. The behavior of these animals differed in no wise from animals receiving 225 mg. per kg. of sodium barbital by vein, animals in both groups remained asleep for over 15 hours.

<sup>1</sup> Klimesch: Arch. f. Exper. Path. u. Pharmakol., 172: 10, 1933.

<sup>2</sup> Klimesch and Starkenstein: Arch. f. Exper. Path. u. Pharmakol., 176, 494, 1934.

<sup>3</sup> Bush: J. Pharmacol. and Exper. Therap., 61, 134, 1937.

<sup>4</sup> Koppanyi, Murphy and Krop: Arch. Inter. Pharmacodyn. Therap., 46, 76, 1933.

This result may be considered as a direct proof that the anesthetic lag following sodium barbital injection is not due to the greater stability of this salt in the blood and tissues.

**The delay of onset of rigidity following oral administration of sulfanilamide in morphinized dogs.** THEODORE KOPPANYI, CHARLES F. MORGAN (by invitation) and A. EARL VIVINO (by invitation). *Georgetown Univ., School of Medicine.* Morphine (10 mg./kg. intramuscularly), delayed the onset of decerebrate rigidity and/or decerebrate restlessness following oral but not following intraperitoneal administration of sulfanilamide. It was postulated that the morphine delay may be due to pylorospasm. The onset of rigidity was, therefore, compared in three groups of animals—controls, morphine-treated dogs, and dogs with the pylorus ligated. Following the oral administration of 3 gm./kg. of sulfanilamide, the following figures were obtained as to the onset of rigidity: controls: 1° 35', 1° 30', 2° 10', 1° 40', 2° 20' and 3° 35'; morphine-treated: 24°, 6° 20', 6° 2', 13° 33', 11° 15', and 11° 45'; pylorus-ligated dogs: no rigidity within 24 hours.

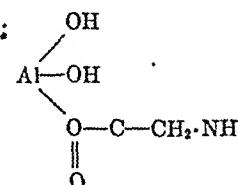
The blood concentrations (Marshall test) showed a close parallelism to the physiological state of the animals. The free sulfanilamide concentration for the controls averaged 298 mg. per 100 cc. of blood after 3 hours, and 194 mg. per cent after 24 hours. For the pylorus-ligated animals the blood values were 14.2 mg. per cent after 3 hours and 97 mg. per cent after 24 hours; for morphine-treated animals the average blood values were 24 mg. per cent after 3 hours and 109 mg. per cent after 24 hours. These observations show that the blood sulfanilamide rises rapidly in controls and declines the following day, whereas the blood sulfanilamide of morphinized and pylorus-ligated animals rises slowly and is much higher the next day. This agrees with the physiological observation that, (a) in morphinized animals the onset of action is delayed and (b) the rigidity is maintained far longer than in the controls.

Following the oral administration of 3 gm. of benzenesulfonylamine, the controls showed rigidity in 55 minutes, and 1 hour and 10 minutes; the morphine animals showed rigidity in 2° 47', 2° 10', and 2° 20'; and the pylorus-ligated dog showed rigidity in 2° 40'.

In resumé, morphine delays the onset of and prolongs the neurotoxic action of sulfanilamide by extending the sojourn of these drugs in the alimentary tract. This should be taken into consideration when sulfonamides are administered to morphinized patients.

**The neutralization of gastric acidity with basic aluminum aminoacetate.** JOHN C. KRANTZ, JR. and (by invitation) DOROTHY V. KIBLER and FREDERICK K. BELL. *Dept. of Pharmacology,*

*School of Medicine, Univ. of Maryland, Baltimore.* It occurred to the authors to attempt to prepare an aluminum salt of an aminoacid which might give the dual effect of immediate acid neutralization by the amino group and secondary prolonged buffering of acid by the metathesis of the aluminum salt of the aminoacid and the strongly dissociated hydrochloric acid. Accordingly aluminum dihydroxy-aminoacetate was prepared which has the following structure



The compound was found to have a prompt and prolonged buffering effect on acid and to be very useful in the treatment of hyperacidity and peptic ulcer. On the basis of the aluminum content, basic aluminum aminoacetate is 42 per cent more efficient in acid-consuming power than dried aluminum hydroxide gel.

**The effect of hypnotics on the action of insulin.** EDWARD LARSON. *Dept. of Pharmacology, Temple Univ. School of Medicine, Philadelphia, Pa.* Since the reported results of hypnotics on the blood sugar are variable (Murphy and Young. J. Physiol. 76: 395, 1932. Goodman and Gilman. The pharmacological basis of therapeutics, pp. 135 and 201, 1941) studies were made on the effect of barbital sodium and morphine sulfate on the blood sugar of the rat in the normal state and also when treated with insulin.

Under standardized conditions, the blood sugars, for five consecutive hours of a group of ten rats, were determined under each of the following conditions: normal, with insulin, with barbital sodium, with barbital sodium plus insulin, with three different doses of morphine sulfate and with these three doses of morphine sulfate plus insulin. The blood sugar of the normal rat, as previously reported by several investigators, is relatively constant. Morphine sulfate (12 mgm. per kgm.) and barbital sodium (0.1 gm. per kgm.) had only a slight depressing action on the blood sugar but when insulin was administered, these drugs in these doses had an anti-insulin action. Morphine sulfate in greater doses, (25 mgm. and 50 mgm. per kgm.) caused variable changes in the blood sugar, in some there was a hypoglycemia and in some, a hyperglycemia. These doses of morphine sulfate intensified the hypoglycemic action of insulin.

**A method of biological assay for the detection of DDT (2,2 bis (p-chlorophenyl 1,1,1 trichloroethane).** EDWIN P. LAUG (introduced by R.

definitely but moved normally when aroused by an adequate stimulus. Since the tetrahydrocannabinol acetate is about six times more active than parahexyl in terms of their effect in the dog (ataxia), the lethal effect is obviously not correlated with the marihuana activity. The enormous doses tolerated without loss of consciousness demonstrate that the conception that the specific central action of marihuana aligns the drug with the hypnotics or narcotics is invalid.

**The sympathomimetic activity of histamine.** DAVID MARSH<sup>1</sup> (by invitation) and ROBERT A. WOODBURY. *Dept. of Pharmacology, Univ. of Georgia School of Medicine, Augusta.* The adrenergic vasodilator activity shown by the intravenous administration of true sympathomimetic agents such as epinephrine and butanefrin after the administration of a sympatholytic agent such as yohimbine or piperidinomethylbenzodioxan (933F) produces the same type of femoral arterial pressure pulse contours in the unanesthetized, decapitated or urethanized cat and dog as those produced by small doses of histamine (1 to 50 micrograms per kg.).

In the atropinized cat the first few injections of butanefrin produce adrenergic vasodilation without the assistance of a sympatholytic agent, while further injections produce only adrenergic vasoconstriction. The administration of ephedrine will markedly reduce or block this primary vasodilation and allow the agent to show only its constrictor activity.

Although histamine certainly produces capillary changes in the rabbit and large doses produce cardiac weakness, many rabbits show enough pre-capillary arteriolar vasoconstriction from its intravenous injection in moderate doses that the net result is a rise in systemic arterial pressure. In such rabbits, butanefrin after complete atropinization generally gives only a rise in pressure and the sympatholytic agents fail to produce reversal of action of adrenergic drugs. In rabbits, which respond to histamine with vasoconstriction followed by delayed vasodilation, butanefrin produces vasodilation in addition to vasoconstriction, but the vasodilator activity of both can be blocked with ephedrine in large amounts (5 mg./kg.). [This study was partially supported by a grant from Eli Lilly & Co.]

**Comparison of blood pressure and serum potassium effects of some sympathomimetic amines.** FOSTER N. MARTIN, JR. (introduced by Ralph G. Smith). *Depts. of Pharmacology, Univ. of Michigan, and The Medical College of the State of South Carolina.* The experiments were performed on cats anesthetized with pentobarbital and atropinized. Blood pressure was recorded with a mercury manometer. Blood samples were taken from an artery before and, as frequently as possible, after the

drug injection. The serum potassium was determined by the method of Hoffman using the Evelyn photoelectric colorimeter and a 600 m $\mu$  filter.

In the compounds studied the intensity of both effects is greatest with epinephrine and decreases with the removal of hydroxyl groups from the ring, the hydroxyl from the side chain, the methyl from the amino group, and on changing the ethyl to a propyl side chain or combinations of these changes. The blood pressure and potassium effects are apparently independent since alteration of chemical structure usually changes one of these effects more than the other and since increase in dosage produces a comparatively greater increase in potassium effect than in blood pressure effect with certain compounds and the reverse with others. The simpler compound, aniline, still produces a potassium increase though the blood pressure falls. n-Amylamine raises the pressure but not the potassium on the first dose, the second dose causing a fall in blood pressure. n-Butylamine in small doses lowers the potassium but raises the blood pressure; in large doses it raises the potassium and lowers the blood pressure. The potassium effect of large doses of butylamine are not altered by ligating the adrenals.

**Assay of testosterone propionate using castrate male rats.** DONALD R. MATHIESON and HARRY W. HAYS (introduced by F. F. Yonkman). *Dept. of Pharmacology, Ciba Pharmaceutical Products, Inc., Summit, N. J.* In order to establish the castrate rat as a test animal for androgen assay it was necessary to determine: (1) the age at which rats could be castrated without waiting for seminal vesicle atrophy, (2) the optimum time for removal of seminal vesicles and (3) the establishment of a dose response curve.

It was found that the optimum time for castration was twenty-six to twenty-nine days of age, since at this time the seminal vesicle growth had not yet been accelerated. Also, rats castrated at this age responded in the same degree to Testosterone propionate from seven to three-hundred and fifty days after castration. If older rats were used, the seminal vesicle regression was slow and irregular and the response to Testosterone propionate was directly proportional to the degree of atrophy.

The maximal effect of Testosterone propionate on seminal vesicle growth was obtained at 72 hours with doses less than one milligram and at 96 hours with one milligram or more. A dose-response curve for Testosterone propionate has been established for doses ranging from 0.10 mg. to 1.00 mg. at 24, 48, 72 and 96 hours. Application of the "t" test showed a significant difference between adjacent as well as alternate groups when the seminal vesicles were removed at 72 hours.

Using the experimental design of Bliss ('44) a

<sup>1</sup> Now at University of West Virginia, Morgantown.

rapid and convenient method of assay has been established for androgens.

Comparison of the influence of morphine and a morphine antagonist, N-allylnormorphine, on the respiration of rat cerebrum. NELCIA MAYER (by invitation) and E. L. McCAWLEY. *Dept. of Pharmacology, Yale Univ., School of Medicine*. One of the most characteristic actions of morphine, aside from analgesia, is its depression of respiration. An analogue, N-allylnormorphine, is an antagonist to most of the actions of morphine. In particular it is a powerful stimulant to respiration depressed by morphine.

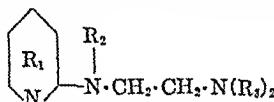
Seavers and Shideman have studied the action of morphine on the respiration of rat cerebrum. In attempting to localize the action of morphine to cellular oxidative and tissue metabolism systems, they found morphine to depress the extra oxygen uptake with added lactate and to a lesser extent with pyruvate, glucose and  $\alpha$ -ketoglutarate.

Using rat cerebrum slices with the Warburg technique we have compared the action of morphine and N-allylnormorphine on the extra oxygen uptake with added p-phenylenediamine (cytochrome oxidase), pyruvate, lactate, succinate and glucose.

Under the concentrations used, 0.003 to 0.015 M, neither drug has any effect on the response produced by added succinate or p-phenylenediamine. With added lactate, pyruvate and glucose, N-allylnormorphine produces a greater depression of oxygen uptake than does morphine. Thus one must look for another explanation than depression of brain tissue respiration to understand the differences in pharmacological action between morphine and N-allylnormorphine.

Antihistaminic and antianaphylactic activity in vitro and in vivo of some  $\alpha$ -aminopyridyl derivatives. RUDOLF L. MAYER, CHARLES P. HUTTRER and CAESAR R. SCHOLZ (introduced by E. Oppenheimer). *Depts. of Bacteriology and Chemistry, Research Division, Ciba Pharmaceutical Products, Inc., Summit, N. J.* Staub (Ann. Inst. Pasteurization 63: 400, 485, 1939) discovered the antihistaminic and antianaphylactic activity of N<sup>1</sup>-phenyl-N<sup>1</sup>-ethyl-N-diethylethylenediamine (1571F). Halpern (Arch. Int. Pharmacodyn. 68: 339, 1942) studied some of its homologues and found N<sup>1</sup>-phenyl-N<sup>1</sup>-ethyl-N-dimethylethylenediamine and N<sup>1</sup>-phenyl-N<sup>1</sup>-benzyl-N-dimethylethylenediamine more active and less toxic for man.

We prepared and studied the activity of certain  $\alpha$ -amino-pyridyl derivatives of the general formula:



1. *Activity in vitro:* Histamine contraction of the guinea pig intestinal strip. In Table I are re-

corded the relative activities of different compounds, assigning an arbitrary value of 1 to compound 63-C, this being the most potent of the series. In the following compounds R<sub>3</sub> represents always CH<sub>2</sub>, R<sub>1</sub> and R<sub>2</sub> varied as indicated.

No.	Compound	Relative activity
$R_1 = \text{pyridyl}$		
63-C	$R_2 = \text{Benzyl}$	1
52-C	$= \text{Phenyl}$	1/100
82-C	$= \text{Isopropyl}$	1/450
84-C	$= \text{Pyridyl}$	Almost 0
$R_2 = \text{benzyl}$		
63-C	$R_1 = \text{Pyridyl}$	1
100-C	$= \alpha\text{-piconilyl}$	1/10
91-C	$= \gamma\text{-piconilyl}$	1/75
74-C	$= \beta\text{-piconilyl}$	1/100

0.01-0.1 $\gamma$  of 63-C per ml. bathliquid prevented the contraction produced by 1 $\gamma$  of histamine diphosphate.

2. *Activity in vivo:* Asthma and convulsions produced by histamine inhalation (Kallos and Pagel, Act. Med. Scand. 91: 292, 1937, Halpern, I.c.). 63-C was about twice as active as the corresponding phenyl-derivative, five times more active than the  $\gamma$ -picoline derivative and one-hundred times more active than the  $\alpha$ -picoline compound.

One-tenth mg. of 63-C per kg., given subcutaneously, protected the majority of animals for two to six hours or more, from histamine convulsions; one mg. per kg. from all signs of convulsions and asthma.

3. *Anaphylactic shock in guinea pigs:* (horse-serum) 0.5 mg. per kg. of 63-C injected subcutaneously, protected all animals from acute and over 50% from sub-acute shock. The protection was almost absolute with 1 mg. per kg. A second shock injection, four days after these prophylactic experiments, proved that the animals were now in a state of antianaphylaxis.

The action of all these substances is specifically directed against histamine (Staub, Halpern, I.c.). The antihistamine activity of 63-C is one-hundred times higher than its antiacetylcholine activity contrary to Trasentine which is 100 times more active against acetylcholine than against histamine.

Variation of chemical substituents on the nitrogen atom of morphine and activity on respiration. E. L. McCAWLEY. *Dept. of Pharmacology, Yale Univ., School of Medicine*. Von Braun has prepared a series of codeine derivatives by varying the radical substituted on the cyclic nitrogen atom. Pharmacologically these compounds may be grouped into codeine-like drugs and codeine (or morphine)

antagonists. These studies are now extended to the morphine series.

Five derivatives of morphine with changes on the nitrogen ring were studied as regards their effect on the respiration of rabbits. N-n-Butylnormorphine produces less depression of respiration than morphine although the duration of action is about the same. Morphine bromomethylate evokes a similar degree of respiration as does morphine, but the activity is of short duration. Normorphine causes a slight depression of respiration followed by a stimulation. N-allylnormorphine administration at dosage of 5 mg./kg. is followed by a stimulation of respiration but respiration is depressed with 20 mgm./kgm.

N-allylnormorphine in doses varying from 0.2 to 20 mgm./kgm. causes an immediate recovery from the narcosis and respiratory depression evoked by 20 mgm./kgm. of morphine; the duration of stimulation of the depressed respiration increases with increasing dosage of N-allylnormorphine. If normorphine antagonizes the depression of respiration by morphine, such antagonism is at best equivocal.

**The effect of p-aminohippuric acid on the bacteriostatic action of sulfanilamide.** A. KATHRINE MILLER (by invitation), ADELLE RANNEFELD (by invitation) and KARL H. BEYER. *Dept. of Pharmacology, Medical-Research Division, Sharp and Dohme, Inc., Glenolden, Penna.* Beyer et al. (Science 100: 107, 1944) have announced that p-aminohippuric acid (PAH) administered with penicillin competes with the latter for a common tubular excretory mechanism thereby causing a retention of penicillin in the body. It is possible that therapeutic advantage would accrue from the combined use of sulfonamides and penicillin, as anticipated by Ungar (Nature, 152: 245, 1943). It follows that this effect would be accentuated by the combined use of PAH and penicillin with the sulfonamide provided the PAH does not possess the antisulfonamide activity of p-aminobenzoic acid (PAB) from which it is derived chemically.

We have compared the effect of PAH with that of PAB on the bacteriostatic action of sulfanilamide (SA) on *Escherichia coli*. Varying concentrations of PAB (M/500 to M/128,000) or PAH (M/50 to M/12,800) were added to tubes of bacto-peptone medium with and without the addition of SA (M/200). Control tubes of unsupplemented bacto-peptone medium were included in each test. The effect of the compounds on the multiplication of *E. coli* was determined by measuring turbidities photoelectrically at the time when growth in the control tubes was just maximal.

Under these conditions neither PAB nor PAH influenced the growth of *E. coli* except at the highest molarities (M/40 PAH stimulated and M/500 PAB somewhat inhibited growth). The almost completely bacteriostatic effect of M/200 SA was not

inhibited to any notable extent by concentration of PAH up to M/50 whereas approximately 60% inhibition occurred in the presence of M/128,000 PAB.

**Comparison of mereuhhydrin with mercupurin as diuretic agents in man.** WALTER MODELL, HARRY GOLD and DONALD A. CLARKE. *Dept. of Pharmacology, Cornell Univ. Medical College, New York, N. Y.* In previous papers we described a method for the quantitative comparison of diuretic agents in ambulant patients with advanced congestive heart failure. The patient is weighed, a dose is given, and its effect determined by the loss of weight about 15 hours later. A week elapses during which time the edema reaccumulates and the initial weight is regained. In this way it is possible to repeat the treatment as many times as necessary in similar states of edema to secure a reliable average response to a given dose as a basis for comparison with other agents used in the same manner. The new mercurial, mereuhhydrin, was compared with mercupurin in this way using 0.5, 1.0, and 2.0 cc. doses intravenously (43 patients), and 1.0 and 2.0 cc. doses intramuscularly (24 patients). The results in 139 intravenous comparisons (278 doses) showed that the two drugs were equally effective, average weight loss 4.5 lbs. for mercupurin, 4.4 lbs. for mereuhhydrin. It was similar for 35 intramuscular comparisons (70 doses); average weight loss 3.9 lbs. for each drug.

Observations on the local irritant action of intramuscular injections in 65 comparisons (130 injections) in 39 patients strongly favored mereuhhydrin, but since subjective symptoms and judgments were involved, this experiment was repeated with the injections made as unknowns ("blind tests"). The key was applied after all analyses were made. There were 20 patients and 35 doses of each drug injected into the biceps or gluteal muscles. The system of grading gave the higher score to the more severe local pain. The average scores for mereuhhydrin were 0.6 and 0.7, and for mercupurin 1.5 and 2.1. Mercuhhydrin, is, therefore, much less painful by intramuscular injection than mercupurin.

**Further studies on the effect of sulfonamides on the central nervous system.** CHARLES F. MORGAN (by invitation), THEODORE KOPPANYI and A. EARL VIVINO (by invitation). *Georgetown Univ., School of Medicine.* This is a continuation of last year's report published in this journal. The investigation was extended to include benzenesulfonylamine, sulfadiazine and sulfamerazine, administered by mouth, and sulfanilamide, sulfapyridine and sulfathiazole, as well as the former drugs, administered intraperitoneally. Dogs were used throughout.

Of the newer drugs studied, only benzenesulfonylamine produced decerebrate rigidity (8 dogs; 3 grams/kg. by mouth), but this rigidity was inter-

rupted by clonic and tonic convulsions. The rigid neck and hind legs may relax upon stroking the facial and sexual skin. Sulfadiazine and sulfamerazine, in doses up to 7.5 grams/kg. by mouth (vomiting was prevented by morphine administration), produced no marked neurotoxic symptoms on the day of administration but clonic epileptiform seizures with salivation developed the next day and the following days. Delayed death often occurred in 3-6 days. Sulfathiazole, sulfadiazine and sulfamerazine, in doses of 1 gram/kg., when given intraperitoneally produced complete analgesia, loss of reflexes, loss of sight and hearing and clonic convulsions within 2 hours following administration. These convulsions, as well as those produced by sulfapyridine, were of periodic nature, e.g., at the beginning they appeared every 10 or 15 minutes, they became more frequent and often stopped several hours before death.

Mydriasis and absence of the light reflex was also demonstrated for sulfathiazole, sulfamerazine and benzenesulfonyl amide. This mydriasis is not an atropine-like action but probably of central origin because moderate doses of pilocarpine instilled produced prompt miosis.

In resumé, sulfanilamide produced rigidity only, benzenesulfonyl amide rigidity and convulsions, the other sulfonamides periodic convulsions only (mainly clonic). The abolition of the light reflex is probably of central origin.

Effect of certain choleretic agents on the cholic acid and cholesterol content of hepatic bile. JAMES L. MORRISON. *Pharmacology Lab., School of Medicine, Emory University, Ga.* The sodium salts of  $\alpha$ -chloropropionic,  $\alpha$ -bromopropionic,  $\alpha$ -bromobutyric,  $\alpha$ -bromoisobutyric,  $\alpha$ -bromovaleric,  $\alpha$ -bromoisovaleric, and  $\alpha$ -hromo-n-caproic acids produce a marked hydrocholeresis in pentobarbitalized dogs within 5-6 minutes after intravenous injection, lasting from 1-5 hours (*Fed. Proc.* 3: 83, 1944). Samples of hepatic bile taken from a common duct cannula were analyzed before and after intravenous injection of the above halogenated fatty acids for cholic acid, cholesterol, and total solids. This was repeated in a series of dogs receiving only intravenous injections of saline. Cholic acid was determined by the method of Irwin (*J. Biol. Chem.* 153: 439, 1944). The total bile excreted during each hour period was combined and used for analysis, samples being taken until the bile flow had returned to normal for at least three hours. Results indicate that with all the agents studied the cholic acid, cholesterol, and total solids vary inversely to the bile flow.

Amphetamine: A special case of sympathomimetic activity. MICHAEL G. MULINOS. *Dept. of Medicine and Pharmacology, New York Medical College.* The pharmacology of amphetamine (Am.) was investigated using the following effects as

criteria of activity. a. The size of the normal, the denervated or the decentralized iris of the rabbit and the iris and nictitating membrane (nm) of the cat. b. Stimulation of the sympathetic nerves to the iris, nm, gut and blood vessels.

Results: a. Am. dilates the intact and the decentralized iris but not the denervated iris of the rabbit. b. Am. contracts the denervated nm of the cat but feebly. c. On the nm, iris, gut and blood vessels, Am. "saturates" the point at which it acts so that more Am. is ineffective yet epinephrine and sympathetic nerve stimulation are as effective as ever. d. Neither nicotine saturation nor recent ganglionectomy abolish the effects of Am. e. Am. at first inhibits the intestine of the pithed cat. A second dose of Am. is usually stimulatory although epinephrine and splanchnic stimulation are still inhibitory. f. Am. intravenously activates the intact iris and nm; raises blood pressure and inhibits the gut, yet it does not dilate the denervated iris or the denervated nm. These it should do through the production of sympathin if it acts on adrenogenic nerves in the classical sense.

From these data it was concluded that amphetamine acts by stimulating those sympathetic nerve endings which act upon the effector cells directly and not upon those which act by way of a mediator.

Effects of benzotriazole on the nervous system. MARK NICKERSON (by invitation) and LOUIS GOODMAN. *Dept. of Pharmacology, Univ. of Utah School of Medicine, Salt Lake City.* The structural similarity between benzimidazole and benzotriazole prompted an investigation of the latter's action on the c.n.s. Experiments on intact and low spinal animals indicate a selective depressant action of benzotriazole (200-300 mg./kg., i.p.) on the spinal cord. Nociceptor cord reflexes are abolished at a time when corneal, pharyngeal, and pinna reflexes are active and the animal appears conscious. Benzotriazole causes less enhancement of two neuronal cord transmission and less decrease in skeletal muscle tone than does benzimidazole. With these doses respiratory exchange is markedly increased. The EEG (rabbits and cats) is unaltered except by very high doses.

Benzotriazole (2.0% solution) is also a potent surface and injection local anesthetic, and does not appear to injure nerve tissue. However, it is irritating to mucosal and subcutaneous tissues.

The cord action of benzotriazole is reflected in the fact that it will protect mice against three or more lethal doses of strychnine. However, metrazol convulsions, although decreased in severity and made more clonic, are greatly prolonged, lasting intermittently for 3-4 hours after a single injection. The duration of the electrically recorded cortical response to subconvulsive doses of metrazol (bursts of rhythmic activity, frequency about 5/sec.) may be increased five times, and after benzotriazole, the

typical EEG seizure pattern produced by convulsant doses of metrazol is less likely to be accompanied by motor activity. [This investigation was supported by a grant from Givaudan-Delawanna, Inc.]

**Studies of the metabolism of 2,2-bis (para-chlorophenyl) 1,1,1-trichloroethane (DDT).** RUTH R. OFNER (by invitation), GEOFFREY WOODARD (by invitation) and HERBERT O. CALVERY. *Division of Pharmacology, Food and Drug Administration, Federal Security Agency, Washington, D. C.* When sublethal doses (50-200 mg./kg.) of DDT are fed to dogs and rabbits, there appears in the urine from 0.3 to 4 mg.% of organically bound chlorine. Approximately 80% of this chlorine is in combination with an acidic material. When the colorimetric method of Schechter and Haller (J. A. C. S. 66: 2129, 1944) which gives characteristic colors with DDT and related compounds became available, it was immediately adapted for use in this study. The color developed with the acidic material gives an absorption curve identical with that obtained from p,p'-dichlorobenzophenone. The vigorous oxidative procedure inherent in the intensive nitration in Schechter's method converts any DDT metabolite possessing the p,p'-dichlorodiphenylmethyl radical with the exception of DDT itself and the 2,2-bis (p-chlorophenyl) 1,1 dichloroethane to the above ketone. In the meantime, White and Sweeney (Pub. Health Rep. 60: 66, 1945) reported the isolation and characterization of this acidic material as 2,2-bis (p-chlorophenyl) acetic acid. We have further studied the remainder of the organically bound chlorine which is neutral in character. DDT if present in the urine would be in this fraction but its presence could not be demonstrated. Upon acid or alkaline hydrolysis an acidic material identical with the above acid is slowly formed. This means that the aliphatic chain of DDT is still intact.

It has also been found that feeding the much less toxic 2,2-bis (p-chlorophenyl) 1,1-dichloroethylene, a possible intermediary metabolite of DDT, results in similar urinary excretory products in the same proportion.

This colorimetric method is recommended for the quantitative study of DDT distribution and metabolism.

**Effects of privine and neosynephrine on the Starling heart-lung preparation.** ERIC OGDEN and G. A. EMERSON. *Univ. of Texas Medical Branch, Galveston.* Administration of privine HCl was previously found to be followed by cardiac irregularities, in doses  $> 10^{-4}$  mM/kg. in the pentobarbitalized dog. (J. Pharmacol., 82: 42, 1944). Cardiac output (by direct measurement and rotameter); arterial and venous pressures, hematocrit and blood volume (Evans' blue) were estimated in heart-lung preparations in which both donor and recipient

dogs were narcotized with pentobarbital, ether, morphine or combinations of these agents. Effects were noted after addition of  $10^{-3} - 10^{-1}$  mM/L. of privine HCl,  $5 \cdot 10^{-3} - 10^{-2}$  mM/L. of neosynephrine HCl and  $10^{-4} - 10^{-3}$  mM/L. of epinephrine HCl. In this preparation privine is without appreciable influence on heart rate. As evidenced by changes in output and venous pressure, even the highest doses of privine had little effect if the venous pressure were low. However, in preparations with rising venous pressure and impending failure even small doses of privine always appeared to show a negative inotropic effect and accelerate the development of failure.

Neosynephrine regularly showed positive inotropic effects at all levels of venous pressure and was without significant effect on heart rate. Epinephrine invariably lowered the venous pressure but no evidence in these experiments indicates how far this was due to cardiac acceleration or how far to a positive inotropic effect.

**The influence of ether and dial upon the penetration of sulfathiazole into the cerebro-spinal fluid.** MERVIN PERDUE (by invitation), CARL SCREWS (by invitation), and R. S. TEAGUE. *Dept. of Physiology and Pharmacology, Univ. of Alabama, School of Medicine.* The use of sulfathiazole in meningitides is limited because of the low concentration reached by the drug in the cerebro-spinal fluid. A study is being made of the influence of certain substances which affect the caliber of cerebral vessels upon the cerebro-spinal fluid concentration of sulfathiazole. For example, the effect of ether, which has been described as a vasodilator for cerebral vessels, has been compared with the effect of dial, which tends to constrict the cerebral vessels. Dogs anesthetized with one or the other anesthetic were given an injection of 10 cc./kg. of a 2.4% solution of sodium sulfathiazole sesquihydrate intraduodenally after ligation of the pylorus. The sulfathiazole levels in the blood and cisternal fluid were determined subsequently each hour for five hours. Although the blood sulfathiazole concentrations in the two groups were identical, the cerebro-spinal fluid levels in dogs anesthetized with ether were 30-40% higher than in those anesthetized with dial. Thus ether increases the penetration of sulfathiazole into the cerebro-spinal fluid. Although it is presumed that this effect occurs by virtue of the increased cerebral vascularity induced by the ether, secretion of sulfathiazole by the choroid plexus as opposed to increased diffusion is not necessarily ruled out. [Aided by the Univ. Research Fund.]

**Effect of digitalis on coagulation time of blood.** HELEN RAMSEY (by invitation), N. W. PINSCHEIMDT (by invitation), and H. B. HAAG. *Dept. of Pharmacology, Medical College of Virginia, Richmond.* Recent publications indicate that the administra-

tion of digitalis decreases the coagulation time of blood. In an extensive series of experiments, in which coagulation time was determined by a modification of the Lee-White method, we obtained the following results:

In dogs maintained under dial or sodium pentobarbital anesthesia the intravenous injection of USP reference tincture of digitalis, diluted 1:15 (1 cc. per Kg. body weight every five minutes) or of gitalin, diluted 1:5000 (0.25 cc. per Kg. every five minutes) resulted eventually in a reduction of coagulation time by approximately 2 minutes (normal coagulation time was about 5 minutes). Almost no change was effected by digitalis administered in the same manner to etherized dogs.

Intravenous administration of one-half the fatal dose of digitalis to trained unanesthetized dogs did not shorten coagulation time.

Daily oral doses of digitalis to toxic amounts to unanesthetized dogs had no effect upon coagulation.

Preadministration of heparin to rats in amount sufficient to render the blood incoagulable did not alter the toxicity of digitalis as determined by the official rat assay method.

*In vitro*, digitalis produced no alteration in coagulability of blood when compared with a control solution of equal alcohol content. These experiments included addition of 0.1 cc. of the diluted tincture (1:10 and 1:100) to 1 cc. of freshly drawn blood from unanesthetized dogs and from dogs under dial anesthesia; addition of similarly diluted digitalis to blood containing varying amounts of heparin; and addition of heparin (1:1000 and 1:2000) to blood containing varying amounts of digitalis.

An *in vitro* method for the evaluation of anti-leishmanial agents<sup>1</sup>, RACHEAL K. REED and HAMILTON H. ANDERSON. Division of Pharmacology and Experimental Therapeutics, Univ. of California Medical School, San Francisco. It has been determined that leishmania, in the form of L. D. bodies remain viable for 30 hours when infected splenic tissue is macerated and suspended in 0.9% sodium chloride solution containing 10% horse serum kept at room temperature (22-25°C.). For the *in vitro* screening of chemicals proposed for trial in leishmaniasis a spleen and liver from an infected Syrian hamster (*Cricetus auratus*) were macerated with sand in a mortar under sterile conditions, and suspended in 20 cc. of saline to which horse serum had been added. The mixture was centrifuged for one minute at 1000 R.P.M. in order to throw down tissue masses. The supernatant fluid containing the L.D. bodies freed from cellular debris was then

used in testing the efficacy of the various drug dilutions. Of the supernatant 0.25 cc. was added to 4.5 cc. of each dilution of the agents under investigation, the concentrations used being 1:1,000; 1:10,000; 1:100,000. The test tubes containing these mixtures were then agitated continuously at the rate of about 60 times per minute, at room temperature during the test.

Samples were taken at 3 and 24 hours from each test tube and air-dried smears made and examined to determine presence of leishmania. At the same time N.N.N. media were inoculated and examined for viability after 7-10 days incubation at room temperature. Horse, not rabbit, blood was used in making the N.N.N. media. Some correlation between this test and *in vivo* trials of drugs in experimentally infected hamsters may exist, especially with such an agent as stilbamidine.

The antianaphylactic and antihistaminic activity and toxicity of N'-pyridyl-N'-benzyl-N-dimethyl ethylenediamine HCl. BARBARA RENNICK (by invitation), DOROTHY CHESS (by invitation), HARRY W. HAYS (by invitation), DONALD MATHIESON (by invitation), RUDOLF L. MAYER (by invitation) and FREDRICK F. YONKMAN. Depts. of Pharmacology and Bacteriology, Research Division, Ciba Pharmaceutical Products, Inc., Summit, N. J. Of several antihistaminic compounds produced Mayer Hutterer and Scholz, Feder, Proc., this issue) N'-pyridyl-N'-benzyl-N-dimethyl ethylenediamine HCl, called Compound 63C for convenience, was very active in preventing certain actions of histamine *in vitro* and *in vivo*. In perfused lungs of guinea pigs it was observed that 25-50 gamma of this compound: (a), protected completely and later, partially, against successive intratracheal injections of 50 gamma of histamine phosphate for approximately fifty minutes; a subsequent dose of 63C was again effective after this interval, (b), protected after a control injection of histamine, (c), protected for a longer interval, probably due to limited egress, when injected during the maximum constricting action of histamine and (d) protected less well when injected simultaneously with histamine.

The perfused lungs of guinea pigs sensitized to horse serum were not protected against the bronchiolar constricting effects of horse serum by 63C in any reasonable dosage. However, some protection was afforded to 3 to 7 pigs thus sensitized when treated with 5-20 mgm./kg. of 63C injected subcutaneously 5-20 minutes before excision of the lungs. Slight protection appeared with the higher doses while four animals were unprotected in the same or lower dose range. 0.1 and 1.0 mgm./kg. afforded no protection when given intratracheally in the perfused, sensitized lung, whereas, histamine was decidedly less constricting following the horse serum.

Wheals produced by intracutaneous injections of

<sup>1</sup> The work described in this paper was done under a contract, recommended by the Committee on Medical Research, between the Office of Scientific Research and Development and the University of California.

0.05 ml. histamine phosphate, 1-1000, into the shaved skin of albino rabbits could be prevented by intravenous administration of 63C, 1.0 mgm./kg., and by gastric instillation, 300 mgm./kg., repeated at 30 minute intervals. This nullifying effect endured for more than 60 minutes. Evans Blue injected intravenously before other drugs, facilitated this study greatly since its extravasation occurred at the site of histamine injection unless adequately protected by 63C; no such extravasation occurred normally after 0.05 ml. intracutaneous injection of 0.85 per cent NaCl solution.

The toxicity of this compound in terms of mgm./kg. and LD<sub>50</sub> has thus far been determined as follows:

White mice, subcutaneously, 30.

White rats, females subcutaneously, 250, intravenously, 10-11.

White rats, males subcutaneously, 350, intravenously, 10-11.

Rabbits, subcutaneously, 33, intravenously, 10-11.

The material is well tolerated by man since between 200 and 500 mgm. (total oral dose) have been ingested by five subjects for 8 to 10 days without undesirable symptoms. Prolonged administration of 63C is now being studied.

**Cardiovascular response of the guinea pig to intravenous injections of histamine, epinephrine and piperidinomethyl-benzodioxan.** C. A. Ross (introduced by C. D. Leake) and DAVID F. MARSII (by invitation). *Dept. of Pharmacology, West Virginia Univ. School of Medicine, Morgantown.* As determined with the Hamilton optical manometer, the normal unanesthetized guinea pig has a heart rate of 280 to 325 beats per minute and carotid arterial blood pressure of 110/70 to 125/76 mm Hg. Five hundred to 800 grams male guinea pigs received 5 mgm./Kg morphine sulfate subcutaneously and one per cent procaine HCl at the site of the introduction of the cannula. Five tenths to 20 micrograms/Kg histamine phosphate intrajugularly produce transient vasodilation with blood pressure dropping to 90/60 to 70/40 with little or no change in heart rate. Larger doses (20 to 50 micrograms/Kg) cause cardiac weakening also. In no case has any evidence of vasoconstriction been found.

Epinephrine (2 to 4 micrograms/Kg) produces vasoconstriction with rises in blood pressure to 130-85 without appreciable change in heart rate. In one instance there was a following delayed vasodilation with a fall in pressure to 98/63 mm Hg. Twenty to 60 micrograms/Kg produce rises as high as 225/130 with the heart rate becoming as slow as 72 beats per minute. Two mg/Kg of 933F partially antagonize the vasoconstriction produced by 10 to 15 micrograms/Kg epinephrine. In no case has the typical epinephrine reversal been observed as is the rule with cats or dogs.

The urethanized cat has a much lower normal

blood pressure and slow heart rate, but the response to epinephrine, histamine and 933F is qualitatively similar to the unanesthetized guinea pig. All animals recovered from the experimental procedures.

**Intrinsic iodine metabolism of the thyroid after thiouracil and thiocyanate.** W. T. SALTER and (b: invitation) E. A. MCKAY. *Labs. of Pharmacology and Toxicology, Yale Univ., School of Medicine.* Thiouracil was administered to adult rats in heavy dosage (0.5 mgm. per kilo per day) for three weeks. This medication was stopped, and during the recovery period the animals were treated with either thiocyanate (1 mgm. per kilo per day) or iodide (0.5 mgm. per kilo per day), or both together. Colateral histological studies were made. The results indicate (a) that dosage is highly important in determining the response of the gland; (b) that the effect of thiouracil and thiocyanate depends upon the iodine supply at pharmacological levels; (c) that there are time lags not only in the failure of hormonal supply to the organism before the action of thiouracil becomes manifest, but also in the recovery of normal glandular function after thiouracil is stopped; and (d) thiouracil and thiocyanate probably exert an influence at different stages in the mechanism of natural hormone synthesis.

The production of colloid by glands poisoned with drugs was studied. The synthesis of thyroid protein ("colloid") can proceed independently of iodine metabolism and independently of endocrine potency.

**Factors affecting blood pressure reversal in ergotamine and yohimbine treated animals.** LLOYD D. SEAGER, M. C. PRUITT (by invitation), H. L. HIPPEL (by invitation) and R. BALDWIN (by invitation). *Depts. of Pharmacology, Woman's Medical College of Pa. and Univ. of Tennessee.* In general the higher the initial blood pressure the greater the reversals to epinephrine obtained in dogs or cats ergotimized or yohimbized. If the pressure is lowered by hemorrhage, vasodilator drugs (nitrites, caffeine, histamine) the reversals become progressively less and disappear entirely at a critical level usually between 40 and 60 mm. Hg. As the pressure is lowered by hemorrhage or vasodilators an initial pressor response may occur and become accentuated as the pressure is further reduced.

The abolition of the reversal phenomenon at low pressures is not due to anoxia as raising a critically low pressure by pituitrin gives a return of the phenomenon. The reversal phenomenon, contrary to the finding of Koppanyi, was not found to be abolished by atropine even in doses up to 100 mg. per kg. Good reversals were obtained under Nembutal, Amytal, Phenobarbital, Barbital, Evipal, and Pentothal anesthesia. Ergotamine and yohimbine in dosages giving reversal to epinephrine were found to abolish asphyxial rises in blood pressure and often reversed the response to overventilation.

**Effect of nephrotoxic doses of quinine and uranium salts on kidney function in the white rat at low barometric pressure.** H. HUMMER SILVERSTEIN. Dept. of Pharmacology, Univ. of Virginia, Charlottesville. Two series of white rats were given daily intraperitoneal injections of 2% quinine-HCl solution (1 cc. per rat), one of which was exposed to a barometric pressure of 282 mm. Hg in decompression chambers for 3 hours daily, while the other series served as a room-pressure control. Quinine-treated animals exposed to low pressures responded by a rapidly-increasing polyuria, from an initial average of less than 1.0 cc. urine per 100 grams body weight per 3-hr. period to an average of over 3.0 cc. at the end of 10 days. Thereafter the condition of the animals rapidly deteriorated and the polyuric response fell off from the maximum; but at the end of 14 days, the average 3-hr. urinary excretion was still almost 2.0 cc. Chloride determinations made on the daily 3-hr. urine samples revealed a great increase in Cl concentration per cc. of urine which was maintained until the end of the experiment. Taken in conjunction with other work reported from this Laboratory, these observations seem to indicate that during exposure to low barometric pressures there is decreased reabsorption of chlorides as well as of water by the renal tubules, which is augmented by the coincidental nephrotoxic action of quinine.

Animals injected with a nephrotoxic dose of uranium nitrate (0.3 mgm. U per rat) showed a marked polyuria at room pressure, which was maintained almost up to the time of death, five or six days later. Other uranium-injected animals, exposed daily for 3 hours to 282 mm. Hg pressure, showed an almost identical polyuric response. Evidently the uranium polyuria was maximal, hence could not be further increased by the anoxia of the renal tubules brought about by high-altitude exposure. [This investigation has been made with the assistance of a grant from the Ella Sachs Plotz Foundation.]

**New aspects of barbiturate activity: effects of neostigmine.** DONALD SLAUGHTER.<sup>1,2</sup> Dept. of Physiology and Pharmacology, Southwestern Medical College, Dallas, Texas. De Nito reported that neostigmine enhanced the depression of the CNS by barbital. Other work indicating that barbiturates possess cholinergic activity suggested testing the effect of neostigmine on their hypnotic activity and on their effect on pressure-pain threshold.

The Eddy method of pressure-pain response was employed. Animals (cats) were carefully observed as to hypnotic effects at 1, 2, 4, 6, or 8 hours after administration of the drug. Sodium barbital, pento-

barbital, seconal, sodium alurate, and a synthetic hypnotic, 3114 "Roche," were used, with and without neostigmine. Tests were conducted so that, for a given drug, a relatively small dose alone was compared with approximately twice that amount alone, and these effects compared with the action of the relatively small dose of neostigmine.

In general, results indicate that neostigmine enhanced the hypnotic effects (ataxia, drowsiness, and full hypnosis) and reduced excitement produced by the drug alone. Exceptions noted were that, in the 1st and 2nd hours only, neostigmine plus sodium alurate decreased drowsiness and neostigmine plus 3114 "Roche" decreased ataxia. Neostigmine also increased the pressure-pain threshold with all drugs used, the average increase being 47.3%, with a range of 37.4 to 60.3%.

**Dark adaptation time following administration of sulfonamides.** DONALD SLAUGHTER<sup>1,2</sup> and JULIAN P. MAIS. Dept. of Pharmacology and Physiology, Univ. of Vermont, College of Medicine, Burlington. Dark adaptation time was determined in eighteen normal volunteers before, during, and after medication with sulfathiazole, sulfadiazine, and sulfanilamide. This was the time required to identify the direction of an oblong test light of  $\log 1.6 \mu$  lamberts brightness, following exposure for three minutes to a bright light of 2.3 lamberts.

The subjects were divided into three groups of six. Group A received four grams of sulfathiazole daily for three days in four doses and group B a similar dosage of sulfadiazine. In group C two subjects received four grams of sulfanilamide for three days, but in four cases the medication period was shortened because of definite toxic manifestations. Adaptometer tests were made three times daily at fifteen minute intervals for several days before and after (control period) as well as during the medication period. Blood levels of free sulfonamides were obtained twice during the medication period, usually on the first and third day. The results are summarized in the following table. Mean dark adaptation times and standard deviations are given.

Group	Drug	Dark adaptation time (seconds)		Blood sulfonamides free mgm.-%
		Control period	Medication period	
A	Sulfathiazole	49 ± 20	57 ± 22	6.0 ± 1.3
B	Sulfadiazine	42 ± 22	37 ± 19	7.6 ± 1.4
C	Sulfanilamide	44 ± 23	67 ± 46	7.0 ± 0.8

As can be calculated from this table, no group revealed a statistically significant difference be-

<sup>1</sup> Now with the Department of Physiology and Pharmacology, Southwestern Medical College, Dallas, Texas.

<sup>2</sup> Made possible by Therapeutics Research Grant No. A-1333 from the American Medical Association.

<sup>1</sup> Aided by a grant from Hoffmann-La Roche Company, Nutley, New Jersey.

<sup>2</sup> Most of this work was done at Baylor University College of Medicine, Dallas, Texas.

tween the adaptation times of the control and medication periods, notwithstanding the fact that in the latter individual values sometimes ran high.

**Use of drugs in motion sickness.** PAUL K. SMITH, Major, AC. *Laby. of Pharmacology and Biochemistry, AAF School of Aviation Medicine, Randolph Field, Texas.* Motion sickness was studied in human subjects who were swing sick and in navigation and flexible gunnery students who were airsick. Most of the drugs were parasympathetic depressants. Results on the swing suggested that hyoscine, hyoscyamine, atropine, homatropine, benzoylscine, benzoyltropine and hyoscine plus prostigmine were all of some value. The drugs were studied in the same doses for their effect on salivation, pulse rate and accommodation. There was a rough correlation between effectiveness in swing sickness and parasympatholytic activity, suggesting that some of the weaker drugs might be effective in larger doses. Of the three most active drugs hyoscine suppressed salivation less than did atropine or hyoscyamine. None produced significant effects on accommodation. The addition of prostigmine to hyoscine abolished the suppression of salivary flow but did not increase the beneficial effect on swing sickness.

In navigation students hyoscine alone was more effective than a mixture of hyoscine, atropine and sodium amytal or a mixture of hyoscine, hyoscyamine and niacin. Hyoscine alone was of value in reducing the incidence of airsickness in flexible gunnery students.

**The effect of digitalization on the coagulation time of the blood in man.** L. SOKOLOFF, M. I. FERRER and A. C. DEGRAFF. *Dept. of Therapeutics, New York Univ. College of Medicine.* The Lee-White blood coagulation time was determined in ten cardiac patients for several days preceding and following onset of oral digitalis therapy with either the U.S.P. XII leaf preparation or digitoxin. One cc. of blood, obtained expeditiously from the antecubital vein, was placed in each of three test tubes 14 mm. x 100 mm., which were jacketed in thermos-jug water baths between 35° and 40°C. After standing for 4 minutes, the first tube was tilted every thirty seconds until the blood failed to flow down the side of the tube. This was repeated for the second and the third, and the time that was required for the blood to fail to flow in the third was considered the coagulation time of the blood. Although the coagulation time fell in four cases, it was slightly increased in five, and unchanged in another. The average time was 9.46 minutes before and 9.50 minutes following digitalization. Analysis of variance was computed and showed that, although the variance between patients was very significant regardless of therapy, the variance within the patients was within the experimental error. These

observations do not support the hypothesis that oral digitalis therapy increases the coagulability of the blood.

**Chronic toxicity of "cumar."** MAYO II. SOLEY and LEONORE GREENBERG (introduced by Hamilton H. Anderson). *Dept. of Medicine and Division of Pharmacology and Experimental Therapeutics, Univ. of California Medical School, San Francisco.* "Cumar" is a complex synthetic resin which was tested for possible chronic toxicity because of its use in the orange industry. Spiridonoff (Fed. Proc. 1: 168, 1942) showed that repeated daily administration of 100 mgm./Kg. of body weight produced toxic effects in mice. The dose used in our study was 10 mgm./Kg. of body weight per day in each of 30 mice which were so treated for 60 days and then observed on a ground fox chow diet for another 30 days. These animals showed the same increase in growth and weight as 30 mice maintained on the diet without "Cumar." There were no evidences of toxicity in the experimental series. There were approximately the same number of deaths in both the control and experimental series of mice (4 and 6 deaths, respectively). The deaths in both series were from such miscellaneous causes as pneumonia, multiple abscesses, and parasites, while in three instances no cause of death could be found. It may be concluded that "Cumar" in a dose of 10 mgm./Kg. of body weight produced no evidence of chronic toxicity in mice. [Supported in part by Food Machinery Corporation, San Jose, California.]

**The use of alkyl-dimethyl-benzyl ammonium chlorides in mosquito control.** CHARLES H. TAFT (introduced by C. D. Leake) and RUSSELL W. STRANDTMANN (by invitation). *Depts. of Pharmacology, and Public Health and Preventive Medicine, Medical School, Univ. of Texas, Galveston.* A mixture of high molecular alkyl-dimethyl-benzyl ammonium chlorides ("Roecal," kindly furnished by the Winthrop Chemical Company) has been tried as a larvicide against *Aedes aegypti* and *Culex quinquefasciatus*. The dilutions of Roecal were made up in tap water and a small amount of peptone was added as food for the larvae.

Under laboratory conditions in 600 cc. beakers against *Culex quinquefasciatus*, Roecal 1:100,000 prevents hatching of eggs, kills larvae of any stage and pupae. Roecal 1:250,000 kills first and second instar larvae, some third and fourth instar larvae and some pupae. Higher dilutions up to 1:1,000,000 reduce the number of larvae.

Against *Aedes aegypti* Roecal 1:100,000 kills first, second and third instar larvae, but has little effect on pupae. Roecal 1:250,000 kills about 80% first instar larvae. The balance do not mature but remain for weeks in the stage in which they were exposed to the drug.

If these results are applicable to field conditions

it would seem that Roccal might be of value in mosquito control.

**The fate of diethylstilbestrol:** Search for a conjugated sulfate of diethylstilbestrol by means of urinary sulfur partitioning. R. S. TEAGUE. *Dept. of Physiology and Pharmacology, Univ. of Alabama, School of Medicine.* A monoglyuronide of diethylstilbestrol has been isolated from rabbit urine by Mazur and Shorr. Since diethylstilbestrol is a phenol, it might be expected to be conjugated with sulfuric acid as well as with glyuronie acid. This point was investigated by a study of the urinary sulfur distribution in animals after administration of the substance. Diethylstilbestrol was given to rats and rabbits in doses of 1.5 Gm./kg. Some rise in the ethereal sulfate fraction was observed in three experiments on groups of rats, but the normal variation was so marked as to cast doubt upon the significance of this increase. In two experiments using rabbits, no rise in this fraction was seen. In both rats and rabbits a fall in the inorganic sulfate occurred, which was interpreted as being due to inanition. In no case was a rise seen in the neutral sulfur fraction. This would seem to rule out the production of a mercapturic acid derivative as a means of detoxification of diethylstilbestrol. It is concluded that little, if any, conjugation of the drug with sulfuric acid occurs in the rat, and probably none at all takes place in the rabbit. [These experiments were done in the Dept. of Pharmacology, Tulane Univ. School of Medicine, aided by a grant from the David Troutman Schwartz Fund.]

Cytological changes in the anterior lobe of the hypophysis under certain experimental conditions. THURLO B. THOMAS (by invitation) and G. A. EMERSON. *Univ. of Texas Medical Branch, Galveston.* The anterior lobe of the pituitary of rabbits and rats has been shown to undergo definite cytological changes during the course of experimental alloxan diabetes. These changes, particularly with regard to degeneration of basophils, have been studied in relation to the cytological appearance of the pituitary, the islands of Langerhans and the adrenal glands in animals subjected to the influence of various surgical and physiological alterations.

A comparison of two synthetic estrogens, tri-p-anisyl chloroethylene and hexestrol. CHARLES R. THOMPSON (by invitation) and HAROLD W. WERNER. *Pharmacology Dept., Research Labs., The Wm. S. Merrell Co., Cincinnati, O.* Assays were conducted by the method of Kahnt and Doisy on olive oil solutions of the estrogens. Subcutaneously 54.5 gamma of tri-p-anisyl chloroethylene were found to be equivalent to 0.35 gamma of hexestrol, and orally 21 gamma were equivalent to 3.0 gamma of hexestrol.

The duration of action of the estrogens was de-

termined for oral and subcutaneous administration by the vaginal smear technic on castrate rats. Subcutaneously 1.0 mg. of tri-p-anisyl chloroethylene produced an effect lasting 53 days and hexestrol an effect lasting 2 days. Orally 1.0 mg. of either tri-p-anisyl chloroethylene or hexestrol exhibited an estrogenic effect lasting 1-1½ days, while the duration of action of 5.0 mg. of tri-p-anisyl chloroethylene was 22 days and a like dose of hexestrol 3 days.

Classified by the method of Emmens (Jour. Endo. 2: 444, 1941) tri-p-anisyl chloroethylene behaved as a proestrogen with an S/L ratio of 20 and hexestrol as a true estrogen with an S/L ratio greater than 100.

Biological assays on abdominal fat from rats administered tri-p-anisyl chloroethylene showed that the fat contained an estrogen. With the exception of one group, where a trace was found, no estrogenic material could be detected in the abdominal fat of rats administered hexestrol.

**Effect of various compounds on the synthesis of acetylcholine.** CLARA TORDA and HANOLD G. WOLFF. *New York Hospital and the Depts. of Medicine (Neurology) and Psychiatry, Cornell Univ. Medical College, New York.* In the presence of serum and spinal fluid from patients with myasthenia gravis less acetylcholine was synthesized than in the presence of serum from healthy subjects (Torda, C., and Wolff, H. G., Science 98: 242, 1943; 100, 200, 1944; J. Clin. Invest., 23: 649, 1944). The effect of various agents on the acetylcholine synthesis was investigated to identify factors modifying this process.

Brains obtained from mice injected with the adrenotropic factor of the pituitary gland synthesized more acetylcholine than the control brains. Estrogenic hormones, pregnenolone, epinephrine, glutathione, cocaine, manganese, some dicarboxylic acids, most intermediary products of carbohydrate metabolism, some amino acids, tobacco virus, methylxanthines, vitamin C and most members of the vitamin B group, thus far investigated, were found to increase the synthesis of acetylcholine. Vitamin E, even in very low concentrations, induced a marked increase of synthesis suggesting that this substance may have a specific action on this process.

Extracts of the thymus and pancreas, most of the steroid substances, vitamins A and K in low and increasing concentrations, vitamin B<sub>1</sub> and D in higher concentrations, camphor, phenols, some aromatic hydrocarbons and some simpler heterocyclic compounds, methylene blue, most alkaloids, some decomposition products of nucleoproteins, some amino acids, lactic acid, and decrease in pH were found to decrease the acetylcholine synthesis.

"Sulfonamide" drugs and acetylsalicylic acid

did not modify the synthesis in the concentrations used.

**Anti-histamine activity and corneal analgetic effect of three new antispasmodic esters.** ELIZABETH TROESCHER-ELAM (introduced by Hamilton H. Anderson). *Division of Pharmacology and Experimental Therapeutics, Univ. of California Medical School, San Francisco.* An antispasmodic agent without the undesirable side effects of atropine is needed; it should have a therapeutic potency similar to that of atropine against acetylcholine, combined with a significant degree of activity against histamine.

Three new antispasmodic esters, along with pavatrione (G. Lehmann and P. K. Knoefel, *J. Pharmacol.* 74: 274, 1942), were directly compared with trasentin with respect to their effectiveness in relaxing histamine contraction of guinea pig ileum *in vitro*. The analgetic effect of the new esters on the rabbit cornea was also investigated.

Two of these esters, the phenyl- $\alpha$ -thienylglycolate and the phenyl- $\alpha$ -thienylacetate of  $\beta$ -diethylaminoethanol hydrochloride, were synthesized by Blieke and Tsao (*J. Am. Chem. Soc.* 66: 1645, 1944); they were further studied by Lands and Nash (*Proc. Soc. Exper. Biol. & Med.* 57: 55, 1944) chiefly for toxicity and activity against acetylcholine and barium chloride. The phenyl- $\alpha$ -thienylglycolate was found to be 4-5 times as effective as trasentin in relaxing histamine contraction; the phenyl- $\alpha$ -thienylacetate was equal to trasentin, while pavatrione was 0.5-0.8 as active. In rabbits both new esters produced corneal analgesia without irritation.

The hydrochloride of  $\beta$ -piperidinoethyl methyl-p-phenylacetate, synthesized by Blieke and Grier (*J. Am. Chem. Soc.* 65: 1725, 1943), was the most active compound (rabbit jejunum, unstimulated) studied by Lewis, Lands and Geiter (*Fed. Proc.* 2: 86, 1943). On guinea pig ileum, this compound was half as active as trasentin against histamine induced spasm, but caused greater amplitude of rhythmic contractions. In rabbits, corneal analgesia was definite for only a short period, and irritation was generally produced. [Supported in part by Frederick Stearns and Co., Detroit.]

**Toxic effects of glutamic and aspartic acid.** K. UNNA and E. E. HOWE (by invitation). *Merck Inst. for Therapeutic Research and the Research Labs. of Merck & Co., Inc., Rahway, N. J.* The effects of intravenous and oral administration of the dicarboxylic amino acids and some related substances have been investigated in dogs. Intravenous infusion of 1+ glutamic acid at rates of 2.5 to 5.0 mgm./kgm./min. (2% neutralized solution) regularly caused nausea and vomiting. The dogs salivated, their pulse rate decreased, and violent and repeated vomiting occurred when an average of  $219 \pm 23$  mgm./kgm. (7 dogs) of the acid had been

injected. 1+ Aspartic acid produced the same toxic manifestations following the infusion of  $19 \pm 32$  mgm./kgm. (7 dogs). The toxicity of the racemic forms did not differ significantly from that of the natural substances: dl glutamic acid  $233 \pm 83$  (4 dogs), dl aspartic acid  $194 \pm 58$  mgm./kgm. (4 dogs). The addition of glycine in amounts double that of the glutamic acid did not reduce the toxic effects. Slowing of the pulse rate and vomiting were not observed when 400 mgm./kgm. glutamic acid were given to dogs anesthetized with pentobarbital.

The desaminated forms, glutaric and succinic acid, were less toxic. On rapid injection (16 mgm./kgm./min.), however, vomiting occurred similar to that following the dicarboxylic amino acids. During the infusion of succinic acid the body temperature usually rose (up to  $1.0^{\circ}\text{F}$ ); the animals were restless, shaking and scratching their ears.

Glutamic and aspartic acid caused vomiting within 2 hours after ingestion of 500, 750 or 1000 mgm./kgm. Glutaric and succinic acid were tolerated at 500 mgm./kgm., vomiting occurred in some dogs after 1000 mgm./kgm. Glycine and l-leucine in doses of 1 gm./kgm. produced no untoward effects.

**The pharmacological behavior of some derivatives of sulfadiazine.** H. B. VAN DYKE, NATALIA A. TUPIKOVA (by invitation), BACON F. CHOW and H. A. WALKER (by invitation). *Dept. of Pharmacology, College of Physicians and Surgeons, Columbia Univ., and the Squibb Inst. for Medical Research, New Brunswick, N. J.* Thirty-seven new sulfadiazine-derivatives in which various aliphatic substituents were introduced into one or more of positions 4, 5 and 6 of the pyrimidine portion of the molecule were investigated. The solubility of the free and  $N^4$ -acetyl substituted compounds was determined in 0.05 M phosphate buffer, pH 6.5, at  $37^{\circ}$ . In the majority, the acetyl derivative was the more soluble. The removal or addition of non-polar groups markedly altered solubility which will be discussed with reference to "free" and  $N^4$ -acetyl derivatives.

The extent to which the various derivatives of sulfadiazine was bound by human plasma albumin was measured. The introduction of one or more aliphatic radicals in positions 4, 5 or 6 of the pyrimidine ring always led to an increased binding of sulfonamide. Specific aliphatic groups appeared to affect the degree of binding.

The absorption and persistence of these sulfonamides were studied in the mouse and monkey to the extent that conclusions can be reached from drug-levels in blood or plasma. The degree of conjugation was also determined in the plasma of monkeys. There were frequent disagreements between the results in mice and those in monkeys.

Poor absorption usually was characteristic of drugs of low solubility but could also characterize much more soluble compounds. Specific aliphatic groups and their position appeared to be the principal factors determining absorption, persistence and magnitude of conjugation. The degree of binding to plasma albumin did not alone determine persistence.

The potency of strophanthin, U.S.P. XII. BERT J. VOS, JR. and HERBERT A. BRAUN. *Division of Pharmacology, Food and Drug Administration, Federal Security Agency, Washington, D. C.* In the Twelfth Revision of the U. S. Pharmacopoeia, which became effective November 1, 1942, the assay method for digitalis and digitalis-like substances was changed from one in which frogs were used as the test animal to one using cats. In the case of digitalis this change together with a simultaneous change in the Digitalis Reference Standard resulted in an appreciable reduction in the potency of official digitalis preparations. This change has received adequate publicity. Less generally recognized is the fact that k-strophanthin and its preparations were simultaneously increased in potency. In this case there has been no change in reference standard and the increase results solely from the fact that the ratio of the lethal dose of k-strophanthin to that of ouabain for cats is different from that for frogs.

Assays of several commercial samples of k-strophanthin (amorphous powder, ampuls, and hypodermic tablets) by both the U.S.P. XI and the U.S.P. XII methods show that k-strophanthin which meets the average requirements of the U.S.P. XI would have to be increased in potency at least 30 per cent in order to conform to the requirements of the U.S.P. XII. In addition the data suggest that all specimens of k-strophanthin may not behave alike in this respect, the apparent potency of some being more affected by the change in assay than that of others.

Influence of oxygen concentration on effects of convulsant drugs. R. P. WALTON and C. B. PREACHER (by invitation). *Dept. of Pharmacology, Medical College of South Carolina.* The extent to which high and low oxygen concentrations affect survival rates and convulsive tendencies with metrazol, strychnine and sodium cyanide has been measured in white mice. Concurrent control groups, matched to obtain identical sex distributions, were observed under ordinary atmospheric conditions. High oxygen atmospheres (95-97% O<sub>2</sub>) significantly raise the LD<sub>50</sub> of metrazol and strychnine (about 15%) without substantially affecting convulsive tendencies; with cyanide, the effect is greater (about 50% increase of LD<sub>50</sub>) and the convulsive tendency is diminished. Lowered oxygen atmospheres (15% O<sub>2</sub>-85% N<sub>2</sub>) also raise the LD<sub>50</sub> of metrazol about 15% and decrease convulsive

tendencies. (Similar effects have been reported by others with insulin). This type of effect with lowered oxygen concentration is less marked in the case of strychnine and not observed at all with cyanide.

Effect of temperature on the toxicity of some vasopressor amines. MARSHALL R. WARREN (by invitation) and HAROLD W. WERNER. *Pharmacology Dept., Research Labs., The Wm. S. Merrell Company, Cincinnati, O.* There are many conflicting data from isolated publications concerning the toxicity of the more common vasopressor amines. Certain experiments in our laboratories have indicated that temperature variations might be partially responsible for these varied results. The present investigation was undertaken to determine to what extent temperature influences the toxicity of certain commercial vasopressor amines.

Two groups of white mice of the Swiss strain, weighing between 16 and 19 grams, were injected subcutaneously and maintained at different temperatures during the course of the experiments. The following LD<sub>50</sub> values, expressed in mgm./kgm. with the standard error calculated according to the method of Miller and Tainter, (Proc. Soc. Exper. Biol. & Med. 57: 261, 1944) were obtained at 26° and 32°C respectively: Ephedrine—600 ± 54.8, 83 ± 8.9; Propadrine—600 ± 49.0, 124 ± 26.3; Benzedrine—42 ± 4.17, 15 ± 1.6; Tuamine—115 ± 11.6, 76 ± 6.5; Vonedrine—540 ± 48.0, 400 ± 37.0, and Privine—170 ± 13.8, 150 ± 11.0.

It is evident from these data that an increased environmental temperature markedly affects the acute subcutaneous toxicity of certain of the amines while it has little or no effect on others.

The measurement of peak inspiratory rates. J. H. WEATHERBY. *School of Aviation Medicine, Naval Air Training Bases, Pensacola, Fla.* Peak inspiratory rates may be measured by means of an orifice plate flow meter used in connection with a photoelectric membrane manometer. The membrane manometer designed and constructed by Dr. W. E. Gilson of Madison, Wis. has been found suitable for this purpose. An opaque vane is attached at right angles to the rubber membrane. The vane interrupts a beam of light falling on a CE-2 photoelectric cell, the output from which is amplified by three No. 6 dry cells connected in series, and actuates the string galvanometer of a Cambridge Electrocardiograph. Fluctuations of the string are recorded photographically in the usual manner on ECG paper. A mercury manometer is connected across the membrane manometer for standardizing the latter and adjusting the tension of the galvanometer string. The flowmeter proper is standardized by measuring the string deflection produced at measured rates of gas flow under constant pressure head and with known pressure differentials. The flowmeter has a capacity ranging from approximately 10 to 1000 liters per

the eighteen remaining cases, there was no significant change in the alpha frequency in thirteen, significant change in the alpha frequency in thirteen, a decrease in 3, and an increase in 2. The alpha percentage was unchanged in ten and an average decrease of 19% was observed in 8.

That the augmented muscle activity was due to a central (probably cortical) action of marihuana was indicated by comparison of electrical activity in muscles of both hindlegs (one of which was denervated) with those of the temporalis muscle in spinal cats with head and brain circulation intact. Respiration was maintained artificially with an apparatus that permitted breathing of air or various mixtures of air and marihuana smoke. During breathing of a light mixture of marihuana and air the slower cortical frequencies (6-9 per second) disappeared. Concurrently, temporalis muscle activity increased. In contrast, no change was seen in the electrical activity of either group of hindleg muscles. During breathing of concentrated marihuana smoke (short of anoxia) slowing of cortical activity with concomitant decrease in muscle electrical activity was observed.

**Effects of various doses of morphine on temperature, pulse and respiration.** EDWIN G. WILLIAMS.<sup>1</sup> Research Dept., U. S. Public Health Service Hospital, Lexington, Ky. Morphine sulfate, in doses of 10, 20, 30, 40, 60, 70, 80, and 100 mgm. was given to post-addict women patients. Each dosage was given to ten patients. Two cc. of normal saline was given to each of ten patients to serve as a control. Temperature (rectal), pulse rate and respiratory rate were taken at hourly intervals from 8:00 A.M. to 10:00 P.M., inclusive, the day before, the day of, and the day following medication. All of these functions were depressed by morphine. Temperature and pulse rate were affected more by 30 mgm. than by any other dose used. Respiration progressively decreased as the dosage was increased.

**The absorption of thiourea from topically applied ointments.** JACOB W. WILLIAMSON (by invitation), MARSHALL R. WARREN (by invitation), and HAROLD W. WERNER. Pharmacology Dept., Research Labs., The Wm. S. Merrell Company, Cincinnati, O. The recent demonstration that thiourea has marked antithyroid action and that it may cause a leucopenia and granulocytopenia raises a question as to the possibility of systemic effects following topical use of ointments containing thiourea as a stabilizing agent for other substances.

Histologic changes in the thyroid provide definite evidence of thiourea action. These were employed as a biological means of measuring absorption of

thiourea for two oil in water emulsion type ointment bases.

Circular wounds, approximately 1 cm. in diameter, were made in the dorsal thoracic region on white rats. The wounds were shielded with cork rings. Samples of approximately 100 mg. of ointment containing thiourea, in concentrations ranging from 0.05% to 10%, were applied to the wounds daily for 2 to 4 weeks. The animals were sacrificed, and thyroids were examined for evidence of thiourea effects.

Typical thyroid changes were produced by ointments containing 1 to 10% thiourea in 2 weeks but not by ointments containing 0.1% or less in 4 weeks. The minimal effective dose of thiourea by this route was approximately 0.5 mg. per 100 gram of body weight per day as compared to about 3.3 mg. given in drinking water as reported by Astwood (*Endocrinology* 32: 210, 1943).

Additional experiments demonstrated complete or partial regression of the thyroid changes between 2 and 6 weeks after discontinuing drug administration. Thiourea action under the conditions of these experiments was not accompanied by a leucopenia or granulocytopenia.

**Acute toxicity of 2-methyl, 2-4 pentanediol.** GEOFFREY WOODARD (introduced by Herbert O. Calvery), VIRGINIA D. JOHNSON (by invitation) and ARTHUR A. NELSON (by invitation). Division of Pharmacology, Food and Drug Administration, Federal Security Agency, Washington, D. C. The compound 2-methyl, 2-4 pentanediol is an organic solvent recently made available in commercial quantities. It is miscible with water and many organic liquids, and is a solvent for many other organic compounds. For these reasons, it seemed advisable to study its acute toxicity. Accordingly, the acute oral doses for four species of animals were determined and compared with similar data on other compounds.

Animal	LD <sub>50</sub> 's in cc./kg.			
	2-2-4 compound	Diethylene glycol	Propylene glycol	Glycerine
Rats .....	4.0	14.8*	21.0*	12.6
Mice.....	4.5	23.7*	23.0*	22.4
Guinea pigs.....	2.8	7.8*	18.0*	
Rabbits.....	3.2			
Mice (intraperitoneal).....	1.5		10.0	

\* Data previously reported from this laboratory.

Symptoms observed within 1 hour after oral administration were loss of muscular coordination progressing into a narcosis lasting several hours. Deaths occurred from 1 to 4 days after dosage, with many occurring on the 3rd day.

Microscopic examination of tissues of rats given

<sup>1</sup> Senior Surgeon, U. S. Public Health Service Director of Research.

$\frac{1}{2}$  the LD<sub>50</sub> per day for 9 days showed: slight hyperplasia of hepatic cells with increase in their basophilic granules, slight hyaline change in centrolobular hepatic cells, and a questionable excess of protein material in renal tubular lumens.

Caution should be exercised in the use of his compound in preparations intended for human use.

The influence of ephedrine on the vasodilating action of epinephrine, ethylnovsuprarenin and pitressin. ROBERT A. WOONBURY, DAVID MARSH<sup>1</sup> by invitation and RAYMOND P. AHLQUIST (by invitation). *Dept. of Pharmacology, Univ. of Georgia School of Medicine, Augusta.* In most but not all dogs and cats, small quantities of epinephrine (0.002 to 0.01 mgm./kgm.) lowered the arterial pressure, reduced standing waves, and increased the rate of pressure descent at any given pressure during diastole. These data constitute proof of vaso-dilation.

Bubble flowmeter studies on dogs with the skin removed from one leg show that epinephrine (0.02 to 0.04 mgm./kgm.) increases blood flow in the skinless leg and simultaneously decreases flow in the control leg at any given blood pressure level. This is interpreted as evidence that epinephrine constricts cutaneous vessels and dilates those in skeletal muscular tissue.

After ephedrine intravenously (5 to 10 mgm./kgm.) epinephrine caused only pressor effects; even larger doses of epinephrine failed to produce the secondary depressor effect. Blood flow remained unchanged or was reduced in the skinless as well as control leg. Ephedrine apparently eliminated or markedly reduced the epinephrine vasodilating action in skeletal muscle.

Ephedrine also eliminated the cutaneous vasodilating action of Pitressin in dogs, (see Ahlquist and Woodbury, these abstracts) and the sympathetic vasodilation of butanefrin in dogs, cats and rabbits.

The effects of ephedrine on the sympathetic nervous system differ from those of ergotoxine in that ephedrine reduces or blocks the depressor effects of the adrenergic drugs that were studied.

Larger doses of ephedrine seem to reduce or even block pressor as well as depressor effects of epinephrine. [This study was partially supported by a grant from Eli Lilly & Co.]

An investigation of the nature and extent of the binding of oxophenarsine (mapharsen) by the red blood cells of rabbit "in vitro" at 37°C. HAROLD N. WRIGHT and LEWIS D. FINE (by invitation). *Dept. of Pharmacology, Univ. of Minnesota Medical School, Minneapolis.* The extent to which oxophenarsine is bound by the red cells of rabbit's blood was determined after continuous mixing for  $\frac{1}{2}$ , 4 or 8 hours. Within the concentration range from

1:1000 to 1:500,000, twenty-eight to 85% of the oxophenarsine was bound by the cells, the amount bound increased with increasing oxophenarsine concentration to the maximum of 85% at 1:5000. This binding was almost as complete in one-half hour as after four or eight hours.

Adsorption played the major role in this binding, as determined by the isotherm equation, but even at the highest concentration, the cells showed little evidence of saturation despite slight hemolysis. The degree of reversibility of the adsorption process at concentrations of 1:10,000, 1:20,000 and 1:50,000, was in all cases greater than 60% after a single resuspension in fresh plasma and with the lowest concentration exceeded 90% after three suspensions.

The extent of the binding of oxophenarsine by various cell components was determined by dialysis after contact with oxophenarsine for one-half hour. Oxophenarsine did not combine with the serum, dialysis through the collodion membrane being 96%. When added to defibrinated blood, 48% dialyzed, consisting of 21% normally present in the serum and 27% reversibly bound to the cells. With laked defibrinated blood, 75% dialyzed. Since 48% of this was normally in the serum or reversibly bound the remaining 27% was attributed to the rôle played by the intact cell membrane. Of the 21% oxophenarsine bound by the laked defibrinated blood 14% was found to be bound by the hemoglobin and approximately 3% was bound by the cell stroma.

The antihistaminic action of N'-pyridyl-N'-benzyl-N-dimethylethylenediamine HCl (63C) in relation to salivation, retraction of the nictitating membrane, mydriasis, lachrymation and blood pressure in cats. FREDRICK F. YONKMAN, DOROTHY CHESS (by invitation), DONALD MATTHESON (by invitation) and NICOLINE HANSEN (by invitation). *Dept. of Pharmacology, Research Division, Ciba Pharmaceutical Products, Inc., Summit, N.J.* Cats of both sexes under urethane, dial-urethane or pentobarbital anesthesia were arranged for mechanical registration of blood pressure, ipsilateral salivary and nictitating membrane responses as previously described (Federation Proceedings: 3: 88, 1944). Mydriasis and lachrymation were observed. Unless otherwise stipulated all drugs were injected directly into the ipsilateral carotid artery on a per kilogram basis. The following results were obtained in 28 experiments:

1. Compound 63C, 10 to 200 gamma, had no effect on normal functions as observed.
2. Histamine, 10 gamma, usually promoted salivation.
3. This effect was nullified by atropine, 0.2 mgm., subcutaneously.
4. This effect was usually nullified by 63C, in a dose of 5 to 10 gamma or more.

<sup>1</sup> Now at the Univ. of West Virginia, Morgantown.

5. Histamine, in any dosage thus far employed, frequently retracted the nictitating membrane.
6. This effect was usually nullified or dampened by 63C, in a dose of 5 to 10 gamma or more.
7. The antisalivary effect of 63C, 10 gamma, against histamine endured for about 30 to 90 minutes.
8. Faradization of the chorda tympanic nerve was still effective in promoting salivation when histamine was nullified by 63C, hence the latter drug differs from atropine in its antisalivary action.
9. Compound 63C seemed to sensitize the secretory response to pilocarpine, 1 to 2 gamma, epinephrine, 10 gamma, and to faradization of the cervical sympathetic and chorda tympanic nerves.
10. Some experiments indicated that the nictitating membrane also seemed to be sensitized, especially to epinephrine and cervical sympathetic faradization.
11. Compound 63C, 10 to 50 gamma, seemed to have no influence on mydriasis induced by histamine, 10 gamma.
12. Compound 63C, 10 to 50 gamma, had no effect on the transient hypotension induced by histamine, 10 gamma.

The protective action of N'-pyridyl-N'-benzyl-N-dimethylethylenediamine HCl (63C) against horse serum anaphylaxis in dogs. FREDRICK F. YONKMAN, HARRY W. HAYS (by invitation) and BARBARA RENNICK (by invitation), Dept. of Pharmacology, Research Division, Ciba Pharmaceutical Products, Inc., Summit, N. J. Six dogs of both sexes were sensitized to horse serum by injecting 1 cc. into the muscles of the buttocks. After 3 to 6 weeks they were anesthetized with sodium pentobarbital and femoral arterial pressure was determined by arterial puncture using the Parkin's technique. The effects of 1 cc. of horse serum intravenously were then studied before and after 3.5 mgm. or less of 63C. The latter compound was also administered by vein, approximately 8 to 30 minutes prior to the horse serum, when used prophylactically.

Anaphylactic reactions occurred in three of six dogs studied and results of a typical case follow:

Dog 4

Date 1944	Procedure	Press.	Pulse	Resp.
11-6	Sensitized			
12-1	Normal	88	84	12
	Horse serum	32	120	42
		3.5 mgm./kg. 63C		
12-5	Normal	100	90	12
	63C	112	120	36
	Horse serum	134	168	12
12-9	Normal	92	120	36
	Horse serum	29	180	42
		1 mgm./kg., 63C		
12-14	Normal	110	180	24
	63C	110	150	12
	Horse serum	44	150	14
		2 mgm./kg., 63C		
12-18	Normal	78	126	13
	63C	97	120	42
	Horse serum	34	120	18
		3.5 mgm./kg. 63C		
12-30	Normal	86	120	10
	63C	102	114	24
	Horse serum	96	120	18

A point of interest was the gradual hypertension that developed in some experiments in which 63C was used in a dosage of 2 to 3.5 mgm./kg. Simultaneously respiration was accelerated, suggesting a central action in this condition. Normally 63C causes a very transient and mild hypotension in the above dosage. This variance of vascular response to 63C in the normal and "sensitized" state does not readily lend itself to explanation but the anticholinergic action of antihistaminic agents might be partially responsible in these experiments. The possibility of adnergic sensitization can not be ignored in this situation since it prevails in cats under treatment with 63C (See accompanying abstract).

Larger doses of 63C have as yet not been used but similar experiments are contemplated after prolonged daily feeding of the compound to sensitized dogs.

## THE AMERICAN SOCIETY FOR EXPERIMENTAL PATHOLOGY

Abstracts of papers presented for the annual meeting scheduled for Cleveland, May 8, 9, 10, 1945. On account of the cancellation of this meeting, all the papers are to be regarded as "read by title". For possible correction in any of the abstracts see the next issue.

Marrow depressant effects of estrogens in dogs. OLGA S. BIERBAUM (by invitation) and CARL V. MOORE. Dept. of Internal Medicine, Washington Univ. School of Medicine. Study has been made of

the hypoplastic anemia produced in dogs by parenteral administration of estrogenic substances. It was determined that equal molecular weights of estrone, estriol, estradiol, and stilbesterol did not

produce comparable degrees of bone marrow depression. The depressant effects of these substances were directly proportional to their estrogenic activity. Furthermore, estrogenically equivalent doses of the four estrogens produced similar degrees of hypoplastic anemia. Their ability to produce changes in the bone marrow, therefore, seems to be related directly to their estrogenic activity.

The changes in peripheral blood and bone marrow followed a definite pattern. In animals which received 5-10,000 rat units per day, leucocytosis usually occurred by the tenth day of the experiment, with counts occasionally as high as 100,000 cells per cu.mm. Concurrently or shortly thereafter, a severe thrombocytopenia developed. Most animals bled from the gastrointestinal and genito-urinary tracts when the platelets were low and an anemia of variable degree resulted. About the sixth or seventh week of injections in those dogs which survived in spite of the thrombocytopenia, the leucocyte count decreased to leucopenic levels, and the anemia became more profound. Changes in the bone marrow seemed to develop in the following order: first, general hyperplasia of all elements, particularly myeloid; second, marked decrease in megakaryocytes; and third, progressive hypoplasia. Areas of extramedullary myelopoiesis were frequently found in the liver and spleen. Animals given smaller doses usually developed leucocytosis and thrombocytopenia from which they recovered even while administration was being continued; they showed no subsequent hematologic abnormality.

All attempts to protect dogs against the marrow depressant effects of these estrogenic preparations failed. High carbohydrate, high protein diets, together with both oral and parenteral administration of the available crystalline B vitamins, crude liver extract, choline, and crude "folic acid" had no protective effect. Simultaneous administration of testosterone did not prevent development of hypoplastic anemia.

**Permeability of muscle to phosphates during shock.** JESSE L. BOLLMAN and EUNICE V. FLOCK (by invitation). *Division of Experimental Medicine, The Mayo Foundation, Rochester, Minn.* The amount of phosphate entering the muscle from the plasma one hour after intravenous administration of sodium diphosphate containing radioactive phosphorus was determined in seven different groups of rats. The preliminary treatment of each group was as follows: 1) no preliminary treatment; 2) complete occlusion of the circulation of the left thigh and leg by a tightly placed rubber band for one hour, the band being removed at the time of the injection of the sodium phosphate; 3) occlusion of the left thigh and both fore legs for one hour received at time of injection; 4)

occlusion of the left thigh for four hours received at time of injection; 5) occlusion of the left thigh for 3.5 hours with release for one hour previous to administration of sodium diphosphate; 6) occlusion of the left thigh and both fore legs for four hours and administration of phosphate at the time of release; 7) occlusion of the left thigh and both fore legs for 3.5 hours with release for one hour previous to administration of phosphate. Animals treated similarly to groups 6 and 7 developed fatal shock with marked hemoconcentration and decreased blood pressure. Animals similar to groups 2, 3, 4, 5 did not develop shock and showed only moderate hemoconcentration in groups 4 and 5.

The amount of phosphate entering the unoccluded muscle of groups 2 to 7 was 58, 45, 83, 96, 83 and 86 per cent of the amount entering similar muscle of normal animals. The amount entering the muscle which had been previously occluded in each of these groups was 96, 83, 169, 224, 162 and 134 per cent of the normal calculated on a basis of dry weight of muscle. Considerable elevation of the phosphate content of the plasma occurred in groups 4, 5, 6 and 7. If the elevated phosphate of the plasma is considered it appears that the unoccluded muscle is much less permeable to plasma phosphate than normal and that the muscle previously occluded is permeable about as much as normal except in groups 6 and 7 when the blood pressure was greatly reduced.

**Comparison of effects of pyridoxine and pantothenic acid deficiency on neurological tissue of swine.** RICHARD H. FOLLIS, JR. and MAXWELL M. WINTROBE. *Depts. of Medicine, Johns Hopkins Univ. and Univ. of Utah.* Acute and chronic dietary deficiencies of pyridoxine or pantothenic acid were produced in young swine. Diets were otherwise adequate. The pathogenesis of changes in the sensory neuron was studied in each group.

Animals deficient in pyridoxine showed demyelination of the peripheral (brachial and sciatic) nerves as the initial change. Chromatolysis or atrophy of the dorsal root ganglion cells and axis cylinder degeneration were not observed at this time. Later, with increasing peripheral demyelination, atrophy of the ganglion cells, axis cylinder degeneration and dorsal root demyelination appeared. Two animals out of 13 studied showed early degenerative changes in fibers of the dorsal columns in the spinal cord.

Animals deficient in pantothenic acid exhibited chromatolysis of the dorsal root ganglion cells as the initial change. Later myelin and axis cylinder degeneration appeared, followed by degeneration of the dorsal root fibers. Changes were found in the ganglion cells of the spinal cord, predominantly in the anterior horns in 4 out of the 18 animals studied.

Since different morphological patterns were found in the early stages of the deficiency among the 2 groups of animals, the hypothesis is presented that pyridoxine and pantothenic acid are concerned with the metabolism of different portions of the sensory neuron. [Aided by grants from the Rockefeller Foundation, Parke Davis & Co., and the Upjohn Co., and carried out in co-operation with the Bur. Animal Indust., U. S. Dept. Agriculture.]

**Studies on thiamine deficiency in rhesus monkeys.** LOUIS D. GREENBERG (by invitation) and JAMES F. RINEHART. *Depts. of Pathology and Pharmacology, Univ. of California Medical School, San Francisco.* The food consumption and weight and blood thiamine levels of Rhesus monkeys on a thiamine deficient diet were followed. Fat content of the basal diet M-3 of Waisman et al. (Archives of Biochem. 4: 265, 1944) was reduced so that it could be compressed into tablets.

Each monkey served as its own control. They were brought to a state of acute deficiency as indicated by anorexia and ataxia and then cured partially or completely by the administration of a single dose of thiamine. The animals were maintained on the regime without additional thiamine until they again became acutely deficient when they were sacrificed and their tissues were analyzed for thiamine. The values in micrograms per gram were: muscle 0.2-0.3; heart 0.3; kidney 0.8-1.3; liver 0.9.

The blood thiamine levels of monkeys receiving thiamine were in the same range (5-10 micrograms/100 cc.) as those found in man. These fell quite precipitously during the first few weeks, on the deficient diet. The weight loss and food consumption closely paralleled the blood thiamine during this period. The administration of a single dose of 0.8 mg. of thiamine per kilogram to 2 and 0.4 mg. to a third acutely deficient monkey, resulted in a prompt increase in their blood thiamine concentrations, food consumption and weight and it required 37 days, 91 days, and 47 days respectively to bring them again to the point of acute deficiency. The blood thiamine values during the acute stage ranged from 2.4-4.8 micrograms per 100 cc. [Aided by a grant from the Christine Breon Fund of the University of California.]

**Repository penicillin excretion studies.** O. M. GRUNZIT, S. B. BINKLEY and E. A. SHARP (by invitation). *Research Labs., Parke, Davis and Company, Detroit, Mich.* Calcium penicillin was incorporated in oil together with absorption delaying substances, as carbowax, glycerol stearate and beeswax. Pitressin tannate was used for its retardation of urinary excretion. Adrenalin hydrochloride or its base was used for its local vasoconstrictor effect.

In dogs the peak of urinary excretion of penicillin from aqueous solutions with or without gelatin

suspension occurred in the first half to one hour after administration. Peanut oil delayed slightly the peak of excretion but did not prolong the excretion over that of aqueous solutions. Peanut oil containing 5-10 per cent carbowax, 1-5 per cent glycerol monostearate, 1-5 per cent beeswax or pitressin tannate 5pressor units delayed the peak excretion to second or third hour, but more significantly spread the excretion of penicillin for a period of 4 to 5 hours. Addition of adrenalin base 0.25 to 0.5 mg. to aqueous or to oil suspension of penicillin with or without repository substances delayed the peak excretion to third, fourth or fifth hours and prolonged satisfactory rate of excretion up to seven to twelve hours with some penicillin being excreted after this period. Addition of adrenalin over 0.5 milligrams per dose further prolonged excretion of penicillin, but in some instances retarded its absorption in initial period below satisfactory blood level concentration.

In human subjects administration of 100,000 Oxford units of calcium penicillin in peanut oil with adrenalin base 0.5 mg. provided a more uniform and as high hourly excretion as compared with beeswax 3 per cent with or without adrenalin base. Satisfactory blood levels occurred with adrenalin base repository substances up to 7 hour periods.

**Uptake of radioactive iron by the red cells in anemias of various etiology. The use of this isotope as a diagnostic tool.** P.F. HAHN. *Dept. of Biochemistry, Vanderbilt Univ. School of Medicine.* Iron tagged with the radioactive isotope has been administered in single small doses to a number of individuals suffering from various disorders in which anemia was either a prominent or the chief symptom. As pointed out several years ago, the absorption and subsequent utilization of iron is in some manner dependent on the need of the organism for the element, and this finding has been amply corroborated in this and other laboratories. In anemic conditions in which there is no deficiency of iron, such as in pernicious anemia, various hemolytic anemias, anemias secondary to neoplastic disease, and those associated with infectious processes, as in normal subjects there is nearly invariably less than 2% of a trial dose of about 15 mg. in the circulating red blood cells a week after ingestion of the iron. In contrast, in chronic hemorrhagic conditions and in anemias associated with malnutrition where the iron intake has been insufficient, as well as in pregnancy the uptake of the test dose is of the order of 20-50%. In a number of instances it has been possible to rule out iron deficiency as a cause of the anemia in patients presenting atypical symptomatology. In one instance it was possible to demonstrate an iron deficiency anemia superimposed on pernicious anemia in a five year old child. In this case it was predicted

that following peak reticulocytic response to specific liver therapy there would be a second reticulocyte response following administration of iron. Such was found to be the case.

Several cases of aplastic and dysplastic anemias were studied and in general there was no indication of iron utilization.

Structural changes in the thyroid glands of patients treated with thiouracil. BÉLA HALPERT, JOHN W. CAVANAUGH (by invitation) and BERT F. KELTZ (by invitation). *Univ. of Oklahoma School of Medicine, Oklahoma City.* Bilateral subtotal thyroidectomy was performed on seven patients with hyperthyroidism. Two had preoperative preparation with thiouracil only, three with Lugol's solution followed by thiouracil, and two with thiouracil followed by Lugol's solution. In most instances the intensity of clinical signs and symptoms was lowered and the pulse and basal metabolic rates were near normal levels and the patients were gaining weight at the time of operation. Morphologic observations were made on routine H and E sections. In the glands removed following administration of thiouracil only, the acinar content stained lightly, was decreased or absent and the cells lining the acini were low or tall columnar. In three patients subtotal thyroidectomy was performed in two stages. In preparation for the first stage Lugol's solution only was given. In preparation for the second stage thiouracil was given. Thus the effects of iodine and thiouracil could be compared and contrasted in the same patient. Following administration of thiouracil the cells of the acini changed from cuboidal to columnar and the colloid disappeared or became considerably less dense, vacuolated, and scalloped. These changes are similar to those seen in patients in a state of active hyperthyroidism, yet clinical manifestations were at a minimum. This variance between structure and function of the thyroid gland following administration of thiouracil is compatible with the assertion that thiouracil inhibits the production of new colloid but does not interfere with the use of the available colloid.

Experimental arterial lesions related to diet and renal insufficiency. RUSSELL L. HOLMAN. *Dept. of Pathology, School of Medicine, Univ. of North Carolina, Chapel Hill.* Experimental lesions of the connective tissue of arteries and of other tissues of dogs (lesions that bear some similarity to the vascular and collagen lesions in human cases of rheumatic arteritis, periarteritis nodosa, lupus erythematosus disseminata, scleroderma, and dermatomyositis) have been produced with regularity by controlling two factors: (1) diet, and (2) renal insufficiency. The method by which renal insufficiency is produced (heavy metal injury, bilateral nephrectomy, leptospira canicola) is relatively unimportant, but impairment of renal

function is essential. A systematic study of the ingredients in the "standard" diet that was being fed at the time these unanticipated lesions occurred has shown that the dietary factor is concentrated in commercial cod liver oil, is heat stable, is not vitamin A, and probably is not vitamin D.

These studies portray another instance of arterial disease related to a disturbance in lipoid metabolism. Some of the healing and healed lesions suggest the possibility that minor degrees of the same process could play a rôle in "arteriosclerosis" (by predisposing to lipoid deposit). [Aided by a grant from The John and Mary R. Markle Foundation.]

Feline pneumonia following inoculation with human nose and throat washings. MANTON E. HOWARD, FRANCIS G. BLAKE and HUGH TATLOCK (by invitation). *Dept. of Internal Medicine, Yale Univ. School of Medicine, New Haven, Conn.* In an attempt to determine the possible relationship existing between atypical pneumonia in man and feline virus pneumonia, nose and throat washings and sputum from patients with the disease were used for intranasal and intratracheal inoculation in cats. Among 6 trials, patchy pneumonia of mild degree occurred in four with the first passage. Attempts to pass to succeeding generations resulted in negative findings by the third generation in one, the second generation in another. One still remains to be passed. In the fourth, successful passage has been established and is the basis of this report. Nose and throat washings obtained on the 8th day of the illness in a patient with atypical pneumonia involving the left lower lobe were instilled intranasally in one cat and injected intratracheally in another. Both animals developed fever. The cat inoculated intranasally, sacrificed on the fifth post-inoculation day, showed but little pneumonia grossly and a bacteriologically sterile pleural effusion. The pleural fluid, and 20 per cent emulsions of the turbinates and of the lungs were passed to 6 cats, 3 normal and 3 which had recovered from previous infection with the feline virus (strain "S"). Two of the recovered animals inoculated with turbinate emulsion or with pleural fluid failed to show any evidence of infection and were held for further studies of immunity, the third which had been inoculated with lung emulsion was found on sacrifice to have a bacterial peritonitis. The normal animals, all sacrificed on the seventh day, showed some inflammation of the turbinates, some tracheitis, and slight pneumonia in one but no pneumonia in the other two. Subsequent passages with lung material failed to produce pneumonia in cats and further transfer was abandoned at the fourth generation. The animal subjected to intratracheal inoculation of nose and throat washings from the patient was sacrificed on the seventh day and showed small areas of pinkish-grey consolidation in the right upper and left

middle lobes. Culture on usual media yielded no growth. The lungs were stored in a lusteroid tube in a dry-ice chest for two years and four months when routine intranasal transfers were again attempted. Eight serial passages have been effected to date. 2.0 cc. of a 5 or 10 per cent emulsion of cat lung instilled intranasally have resulted in fever and the production of rather widespread greyish-pink consolidation throughout the lungs. Histologically the picture is that of an interstitial pneumonia with the presence of edema and variable numbers of large and small mononuclear cells. The infecting agent passes a Seitz filter and by the sixth passage a  $10^{-6}$  dilution was capable of producing the disease. Cross inoculations in animals recovered from the "S" strain of feline virus and vice versa showed it to be the same agent as that producing feline virus pneumonia. By the time neutralization studies were attempted, the sera collected from the patient were 2½ years old and the results were suggestive but not conclusive. At this time it is not clear whether this virus came from the patient or whether it was latent in cats and became activated by passage.

**Protein metabolism and protein reserves during acute injury from turpentine injection.** SIDNEY C. MADDEN. *Dcpt. of Pathology, Univ. of Rochester School of Medicine and Dentistry, Rochester, N. Y.* Normal adult dogs were given proteinless diet plus casein, 80 calories per kilo, 0.4 gram nitrogen per kilo per day. When fairly steady nitrogen and weight equilibrium had been achieved subcutaneous injection of turpentine was used to produce sterile controlled inflammation. The reaction is characterized by local swelling, induration, and abscess formation, terminated by rupture or incision in 3-4 days, and by general reactions of fever, leucocytosis, and excess urinary nitrogen.

If no change in the diet regime was made nitrogen balance was strongly negative. If the diet nitrogen was doubled and intake insured by spoon feeding equilibrium or positive balance was achieved. An amino acid mixture (ten growth essential amino acids plus glycine) in 10 per cent solution by vein plus glucose intravenously or proteinless diet by mouth were likewise associated with equilibrium or positive balance when the intake was doubled. Protein depleted dogs showed no excess urinary nitrogen on injury and were maintained in balance without increased intake.

The direct relation between increased nitrogen excretion with injury and the existence of protein reserves is reaffirmed. Protection of protein reserves during injury appears possible by adequate intake of nitrogen. These findings do not support recent theories postulating an inhibition of protein anabolism immediately after injury.

**The effect of the intravenous administration of calcium ribonate on parathyroidectomized**

normal dogs.

STEPHEN MADDOCK (and by invitation) DOROTHY JENSEN. *Boston City Hospital, Boston, Mass.* In the course of some experiments on the effect of the removal of various endocrine glands on the serum phosphatase of dogs, we attempted to maintain life by calcium therapy alone. The ordinary preparations available proved difficult to manage. Intramuscular injections produced swelling and tenderness after the first few days and intravenous administration was so fleeting that multiple daily injections were necessary. It was suggested to us that a preparation of calcium ribonate was available and on trial of this salt it was found that a single intravenous dose of 125 mg. per kilo usually sufficed to keep the dogs in good condition for 24 hours.

This result seemed sufficiently surprising to make it worth while investigating the effects of the salt on normal animals.

In all 18 healthy adult dogs, 12 normal and 6 thyroparathoidectomized, were studied. Each normal animal was used to compare the rate of disappearance of intravenously injected calcium gluconate and calcium ribonate.

When the dogs received calcium gluconate the serum Ca returned quite close to the control level at 2 hours and was slightly below the control at 4 hours. With calcium ribonate the values remained 40 to 50 per cent above the control for 6 hours and were appreciably elevated for 10 hours.

There is no very obvious explanation for the difference in the action of the two salts studied.

**Antigenic relationship between normal and leukemic leukocytes.** RUTH A. MARTIN (by invitation), BERNHARD STEINBERG and S. NOWAKOWSKY. *Toledo Hospital Inst. of Medical Research, Toledo, O.* Antibodies were produced against leukocytes obtained from normal people and from patients with lymphoid and myeloid leukemia as well as against lymphocytes from a normal lymph node. Since it was impossible to obtain leukocytic suspensions made up entirely of granulocytes or lymphocytes, antibodies against each type of cell were adsorbed from the antisera. Antibodies against lymphocytes were removed from the granulocytic antiserum. Antibodies against myelocytes were adsorbed from the antilymphatic leukemia and normal lymph node antiserum. Agglutination reactions indicated the presence of individual antibodies for lymphocytes and for leukocytes of the granulocytic series. Antiserum against lymphocytes from which antigranulocyte antibodies were adsorbed did not show a diminution of the titre against lymphocytes. Antibodies against normal leukocytes agglutinated leukemic lymphocytes and myelocytes. The experiments suggest that there is no antigenic difference between circulating leukocytes obtained from normal and from leukemic individuals. However, there

is an antigenic difference between lymphocytes and granulocytes.

Further studies on the mechanisms of injury and fever with inflammation. VALY MENKIN. *Dept. of Pathology, Duke Univ. School of Medicine, Durham, N. C.* In earlier studies the writer has demonstrated the presence of a factor capable of inducing injury in inflammatory exudates. This factor is either a euglobulin or it is associated with that fraction of exudate. To it the name necrosin has been assigned. There is some preliminary evidence that necrosin may be a proteolytic enzyme. Further studies indicate that necrosin is usually recovered from exudates at an acid pH but it is usually absent in exudates at an alkaline pH. Since earlier work indicates that the degree of local injury in inflammation is directly related to the rise in hydrogen ion concentration, the present type of correlation is significant in our further understanding of the mechanism that aids in explaining the reaction of injury with inflammation, namely the additional liberation of necrosin. The repeated injections of this substance into the circulation of dogs is accompanied by pronounced injury to the liver parenchyma in the form of what appears to be a curious zonal denudation of the cytoplasm of liver cells. The correlation of the pH of the exudative material with necrosin formation is also correlated in the same manner with the presence in exudates of pyrexin, the factor concerned in the primary mechanism of fever. When the exudate is alkaline there usually seems to be an absence of pyrexin in contrast to the presence of this substance in acid exudate. This parallelism is of significance since recent studies indicate that pyrexin production seems related to the activity of necrosin.

Production of bladder stones and bladder tumors in rats by feeding of diethylene glycol. ARTHUR A. NELSON, O. GARTH FITZHUGH (by invitation) and HERBERT O. CALVERT (by invitation). *Division of Pharmacology, Food and Drug Administration, Federal Security Agency, Washington, D. C.* Groups of male Osborne-Mendel rats, 12 on each dosage level of 4, 2, and 1 per cent diethylene glycol mixed in the diet, developed bladder stones on the 4 per cent level after 32 weeks and bladder tumors after 53 weeks. At the end of the 24 month experimental period the numbers in each group with bladder stones were 11, 7 and 1 respectively, while the bladder tumors (simple epithelial hyperplasias are not included) numbered 5, 6 and 0 respectively. The longer survival of the rats on 2 per cent probably accounts for their relatively greater incidence of tumors. The stones were polyhedral or ovoid, light tan in color, slightly rough; they were usually multiple and from 1 to 6 mm. in diameter. Of the 11 tumors, most were single or multiple fibropapillomas of around 6 mm.

diameter; sometimes they were numerous enough to make a cauliflower-like mass which together with the stones would markedly distend the bladder. One tumor was a carcinoma composed chiefly of two masses each 1.2 cm. in diameter, which had extended through the bladder wall to neighboring structures and had metastasized to a perirenal lymph node. Another example was composed of two intramural leiomyofibromas, the largest 2.2 x 1.4 x 1.2 cm.; this was the only intramural tumor and the only one not associated with bladder stones at autopsy. Triethylene glycol was given to similar numbers of rats at similar dosage levels, and one group of 12 rats received no glycol; neither group developed bladder tumors or stones.

Histopathologic changes in tissues of children whose dietary protein was insufficient to sustain life. ANDERSON NETTLESHIP. *Univ. of Indiana Medical School, Indianapolis.* The histologic changes were studied in the tissues of four children, ages 1 year 3 months to 7 years, who had died, as nearly as could be determined, of protein starvation. These children came from a class of people whose chief article of diet is polished rice and fruit, occasionally supplemented by black beans and fish. While their precise dietary ingredients could not be determined clinically, no disease other than dietary deficiency could be found. Pathologically there were no major infections or parasitic disease, and histologically the tissues showed no evidence of infection.

Microscopically all of the tissues showed a widespread non-inflammatory interstitial and intercellular edema which was both proteinous, and in some tissues, non-proteinous in character. This was most evident in the loose connective tissues, lymph nodes and lungs. There was marked cytoplasmic loss, compensated for in part by the intercellular edema. The nuclei were crowded together, the karyoplasm condensed and overstained. This was most marked in the heart and adrenals. The fat tissue in the body was depleted and collapsed. There were small superficial ulcerations in the small intestine and lymphocytic infiltrations in the mucosa. The adrenal showed medullary loss. The liver lesion was a widespread fatty infiltration of an extreme grade. In addition, in two cases, there were scattered flocks of necrosis with polynuclear infiltration. This lesion is strikingly similar to that reported in various experimental dietary deficiencies. While no certainty exists as to the exact factor which is lacking in these children, such findings as the above, under the circumstances reported, leaves little doubt but what dietary protein or related compounds when lacking, in children, may produce such lesions. [The author is indebted to The John and Mary Markle Foundation and The American Association of Medical Colleges

whose generous financial aid made it possible to study these cases.]

A toxicologic study of histamine antagonist  $\beta$ -dimethylaminoethyl benzhydryl ether hydrochloride (benadryl). GEORGE RIEVESCHL, JR. (by invitation) and O. M. GRUHZIT. Research Labs., Parke, Davis & Co., Detroit, Mich. Benadryl is under investigation as a drug capable of inhibiting physiological effects of histamine. The preliminary results of acute toxicity studies give the LD-50 in mg./kg. for mice intraperitoneally and subcutaneously as 82 and 130. The intravenous LD-50 for rats, rabbits and dogs was 45.7, 10.5 and 30 mg./kg., respectively. The oral LD-50 in mice and rats was 167 and 545 mg./kg. Lethal doses by all routes produced violent excitement, convulsions and respiratory failure in a short time.

Chronic oral toxicity in adult dogs was studied at dose levels of 10, 25, 40, and 60 mg./kg. per day for approximately 43 days. No progressive changes were noted in the blood counts, hemoglobin and non-protein nitrogen values. The drug did not affect the eating habits of the dogs and there was no significant change in weight. It had no or only a mild emetic effect. At the 40 and 60 mg./kg. levels salivation developed which became a conditioned reflex. The 10 mg./kg. dose produced no apparent symptoms of nervousness, excitement or irritability in dogs. Higher doses caused nervousness, ataxia, gastrointestinal reactions and hyperesthesia of skin.

Autopsy of the dogs receiving 10 to 25 mg./kg. orally revealed no gross pathologic changes. Histologic examination of tissues of the liver, kidneys, spleen, pancreas, adrenals, heart muscle, brain, gall bladder, urinary bladder of gastrointestinal mucosa showed no acute or chronic degenerative processes. The central nervous system tissues were free of congestion, edema, petechial hemorrhages or necrotic cells. Death of animals was primarily associated with respiratory system failure.

**Effect of radiation on malaria.** An experimental study in the chick and duck. R. H. RIDON, Dept. of Pathology, Univ. of Arkansas, School of Medicine, Little Rock, and HILLYER RUDISELL, JR. (by invitation). Dept. of Radiology, Medical College of South Carolina, Charleston. The effect of roentgen irradiation on *P. lophurae* was studied *in vitro* and *in vivo*. In the former experiments parasitized blood from chicks was irradiated and then injected intravenously into young chicks. The degree of parasitemia decreased with the increase in the amount of irradiation. The course of the malarial infection was followed by counting the number of parasitized cells per 500 red cells.

The *in vitro* studies were made by infecting chicks with *P. lophurae* and irradiating the entire body with different amounts of roentgen rays and at varying intervals after the inoculation. The degree

of parasitemia decreased in the treated chicks when compared with the controls.

The effect of radium in the form of radium bromide was studied on *P. lophurae* both *in vitro* and *in vivo*. No effect on the parasitemia was demonstrated in any of these experiments.

**Factors influencing agglutination of leukocytes by antileukocytic sera.** BERNHARD STEINBERG and RUTH A. MARTIN (by invitation). Toledo Hospital Inst. of Medical Research, Toledo, O. Several factors including temperature, centrifugation, presence of electrolytes, age and washing of leukocytes, were investigated to determine the effect on agglutination of circulating leukocytes by antileukocytic sera. Refrigeration at 8°C. completely inhibited agglutination. The velocity of the reaction was maximum at temperatures between 22 and 26°C. and was decreased at higher temperatures. Centrifugation accelerated the rate of agglutination. Electrolytes were found to be essential in definite proportions for the reaction. Age of leukocytes stored in the refrigerator appeared to decrease the degree of agglutination after the 4th day and interfered with it more appreciably after the 10th to the 14th day.

On the basis of these investigations the following is the optimum technic of agglutination of leukocytes. One to four day old leukocytes, 27,000 per cu. mm. in number in 0.05 cc. of normal salt solution are added to 0.5 cc. of inactivated antiserum diluted with normal salt solution at least in the ratio of 1:10. The suspension is agitated for a period of 1 to 3 minutes and then centrifuged for 1 minute at 1600 revolutions per minute. The entire procedure is carried out at room temperature. The tubes are shaken gently three times before reading. Excessive shaking breaks up the clumps. The readings are made immediately after centrifuging. A slight accentuation in the size of the clumps is present at the end of one hour with some leukocytes.

**The blood protein tyrosine test (serum euglobulin) in malaria.** Lt. Col. WILLIAM B. WARTMAN, M.C., A.U.S., on leave of absence from the Inst. of Pathology, Western Reserve Univ., and (by invitation) CAPT. NATHAN SHIMOVITZ, M.C., A.U.S. The purpose of this investigation was to determine the usefulness of the blood protein tyrosine reaction (serum euglobulin) in the diagnosis of malaria. One hundred and ten soldiers with clinical evidence of malaria (*P. vivax*) and positive blood smears were studied three months after removal to a temperate, non-malarious district. They had been in a highly malarious district under combat conditions for four months and received the usual suppressive or symptomatic treatment. In this group of patients and under the conditions of the experiment, the test was not of diagnostic value. Forty per cent of patients had a normal protein tyrosine level at a time when plasmodia were

demonstrable in peripheral blood. It was also impossible to predict relapse by means of the test. High protein tyrosine levels showed a tendency to return to normal within a few months.

Proske and Watson (1939) have reported that, in a different group of patients, protein tyrosine was elevated in 97% of cases of clinical malaria and that a rise indicated a relapse. Since their patients lived and were tested in a malarious area, the possibility of reinfection could not be excluded. It is suggested that the seeming disparity between our results and those of Proske and Watson may indicate an important feature of malaria. If blood protein tyrosine is increased in chronic malaria in endemic areas and not in patients with relatively acute malaria and not subject to reinfection, then some important alteration has occurred in blood proteins, the nature of which is unknown.

Experimental infection of the rabbit's eye with *Torula histolytica*. CHARLES WEISS,<sup>1</sup> ISABELLA H. PERRY (by invitation) and MARION C. SHEVKY (by invitation). *Research Labs. of the Mount Zion Hospital, San Francisco, and the Dept. of Pathology, Univ. of California.* A culture of *Torula histolytica* was isolated from a human eye and injected into the anterior chambers of the eyes of rabbits. This technic permitted the observation of very early pathologic changes. The inferior part of the anterior chamber became opaque and a pannus developed on the surface of the cornea.

Histologically there was a slight exudate consisting of polymorphonuclears and some monocytes along the periphery of the cornea. Along the anterior surface of the iris and the posterior surface of the cornea there was a delicate festoon of rosettes. In the center of each rosette there was a *Torula* organism, surrounded by a single row of cells (polymorphonuclears and monocytes). *Torula* were seen engulfed inside of macrophages.

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Plasma protein metabolism—electrophoretic studies. LOUIS J. ZELDIS (introduced by Sidney C. Madden). *Dept. of Pathology, Univ. of Rochester.* Electrophoretic patterns of normal dog plasma in veronal buffer at pH 8.5 are shown to be essentially similar to patterns of human plasma. Dog albumin has a higher mobility than human albumin and in a mixture of dog and human plasmas migrates as a partially separated peak. Normal dog plasma frequently shows four alpha globulin peaks.

Rates of restoration of plasma protein components in dogs subject to acute plasmapheresis have been studied by electrophoresis. During the first 24 hours following such acute depletion, appreciable quantities of all electrophoretic components of the plasma proteins enter the circulating blood stream even when food is not given and has not been given for 12 hours before plasmapheresis. Alpha and beta globulins are restored more rapidly than other components. In such fasting periods albumin and total globulin appear in approximately the proportions present in normal plasma. Alpha and beta globulins continue relatively elevated during subsequent days in which caloric and protein intakes are adequate for weight and nitrogen gains. Initial albumin levels, however, are regained more slowly than those of total globulin.

The relative proportions of the electrophoretic components of plasma proteins may be disturbed from normal following a single acute depletion for as long as two to three weeks after the total protein level has returned to normal.

Abnormally high beta globulin and fibrinogen, but a low albumin are found in a dog with an acute and chronic cholangitis and hepatitis. Similar elevation of gamma globulin is noted in a dog in which a hemolytic reaction occurred.

## THE AMERICAN INSTITUTE OF NUTRITION

Abstracts of papers presented for the annual meeting scheduled for Cleveland, May 8, 9, 10, 1945. On account of the cancellation of this meeting, all the papers are to be regarded as "read by title". For possible correction in any of the abstracts see the next issue.

The effects of change from a poor to a good diet measured by growth, calcium storage, and hemoglobin levels. BERTLYN BOSLEY (by invitation) and GRACE MACLEOD. *Nutrition Lab., Teachers College, Columbia Univ., New York City.* One group of 28-day-old male and female offspring of albino rats fed a poor diet (duplicating that found in use by school children from low-income families)

were fed this poor diet until they were 73 days old (corresponding to 6 years in human life) and then placed on a good diet (Sherman's Diet 13). A second group was continued on the poor diet until they were 146 days old (12 years in human life), then changed to the good diet. A third group, offspring of animals fed the good diet, were continued on the good diet and served as controls. Animals were

weighed weekly and hemoglobin determinations made bi-weekly. All animals were killed at 194 days of age (16 years in human life) and the calcium content of the bodies determined.

Animals changed to the good diet at the earlier age were slightly heavier at 194 days and had stored more calcium than those changed later. Neither group weighed as much nor had stored as much calcium as the control animals. Hemoglobin increased rapidly after the change in diet and had reached similar levels in all three groups of 194-day-old animals.

The slow gains in weight on the poor diet are typical of the sub-normal increases in weight of children living on poor diets. The low calcium stores of the rats on the poor diet find some counterpart in the poor calcification revealed by X-ray examination of the bodies of such children.

**The use of mice for the measurement of the growth promoting quality of proteins.** D. K. BOSSHARDT, L. C. YDSE, M. M. ARRES, I. S. WESTFALL and E. D. WEISS (introduced by R. H. Barnes). From the Dept. of Biochemical Research, Medical-Research Division, Sharp & Dohme, Inc., Glenolden, Pa. The method of Osborne, Mendel and Ferry for the measurement of protein efficiency ratios (grams gain in weight per gram of protein ingested) has been adapted for use with mice. Three protein sources, defatted dried whole eggs, casein, and wheat gluten were employed for the establishment of conditions for calculating the protein efficiency ratios. These protein sources were fed *ad libitum* to groups of 7 mice at 8 different levels in the diets. Body weight gain, carcass protein gain, protein consumption and digestibility measurements were made.

The ratio of body weight gain to protein consumed at each level of protein was found to be most constant from the 7th to the 10th day after commencing the test feeding period. Choice of a satisfactory test period is somewhat arbitrary, but it would appear that the best time for the establishment of the efficiency ratio is between 1 and 3 weeks. A fraction of the time is required for the establishment of the protein efficiency ratio and a very small amount of the test protein is necessary with the mouse assay as compared with the more conventional rat assay. The absolute efficiency ratios are not the same for both rats and mice, but the results of a large number of assays indicate that proteins fall in the same order of classification by the 2 methods.

**The nutritive value of fats.** R. K. BOUTWELL (by invitation), R. P. GEYER (by invitation) and E. B. HART. Dept. of Biochemistry, College of Agriculture, Univ. of Wisconsin, Madison. Studies were made with weanling rats on the growth promoting value of fats amply enriched with fat soluble vitamins. It was indicated that improved

growth effected by the substitution of butter fat for corn oil in certain rations was due to an increase in the B vitamins available to the rat from the intestinal tract. This conclusion was reached from growth data obtained when butter fat or corn oil was fed in combination with 10 different carbohydrates and at 3 distinct levels of B vitamins. The fat soluble vitamins, salts and casein portions of the ration were kept constant throughout.

Rats on purified diets which contained a medium but not excessive levels of B vitamins maintained a normal growth rate if fed butter fat in combination with the following carbohydrates: starch, dextrin, dextro-maltose, sucrose and a mixture of equal parts of fructose and glucose. Growth was subnormal if corn oil was substituted for butter fat in these rations. In contrast, equal and excellent growth was produced on any of the possible fat-carbohydrate combinations by a 3-fold increase of synthetic B vitamins plus the addition of a liver concentrate as a source of unknown nutritional factors.

Laetose tended to follow the pattern of the above carbohydrates, except the overall growth was poorer. Normal growth was approached with either fat at the higher level of vitamins including a liver powder.

The two fats in combination with a mixture of glucose and galactose or glucose and galactose alone, were comparable in nutritive value at all levels of vitamins.

**The respiratory quotient and blood pyruvate and lactate after ingestion of glucose or fructose by diabetic patients.** THORNE M. CARPENTER, HOWARD F. Root and ELMER STOTZ (by invitation). Nutrition Lab., New England Deaconess Hospital and Harvard Medical School, Boston, Mass. The respiratory quotient (R.Q.), the blood sugar, and the pyruvate (PA) and lactate (LA) levels of the blood were determined in diabetic patients before and after the oral ingestion of 50 grams of glucose or fructose. In a group of 26 patients who had been without insulin for varying lengths of time preceding the tests, slight rises in R.Q. after ingestion of glucose were not generally accompanied by rises in PA and LA, but when the rise in R.Q. was 0.05 or over, there was usually a rise in either PA or LA or both. With one exception, when there was no rise in R.Q. there were no significant changes in the acid levels of the blood. In a group of 20 patients, when insulin was given immediately preceding or immediately following the ingestion of glucose, the majority showed rises in the R.Q. and acid levels of the blood, and these changes were in some patients larger than would occur with the majority of normal subjects. The ingestion of 50 grams of fructose by 15 patients produced a rise in R.Q. in 10 of them, and in all of them the PA and LA levels were increased even when no rise in

R.Q. took place. The rises in R.Q. and organic acid levels of the blood were, in general, larger than after the same amount of glucose. The intermediary metabolism of fructose is, with diabetic patients as with normal subjects, different from that of glucose.

Vitamin E and brownish discoloration of adipose tissue in rats fed diets high in cod liver oil. H. DAM and K. E. MASON. *Depts. of Biochemistry and Anatomy, Univ. of Rochester School of Medicine and Dentistry, Rochester, N. Y.* Rats reared from weaning on diets low in vitamin E and containing 20% cod liver oil (but not diets containing 20% benzol extract of hog liver, or 2% cod liver oil) exhibited a brownish discoloration of the adipose tissue, apparent grossly as early as the 42nd day and increasing slowly with continued feeding. Histological changes, demonstrable to a minor degree as early as the 10th or 15th days, were characterized by phagocytosis of irregular sized globules of brownish fat (probably fatty acids of unknown composition) by developing fat cells which eventually formed compact clusters irregularly interspersed between normal adipose tissue cells. Sometimes pigmented fat accumulated as a ring at the periphery of large droplets of neutral fat. In their acid-fast and other staining reactions these globules resembled the pigment occurring, usually at a later stage, in the musculature and elsewhere in the E deficient rat, and the "ceroid" pigment of nutritional cirrhosis in rats. Rats reared for 5-6 months on E deficient diets and subsequently fed a 20% cod liver oil diet for 4 months showed only minor changes, due probably to a natural decrease in the number of developing fat cells at this age.

These fat changes were readily prevented by tocopherol feeding but, once well established, were reduced to some extent in subcutaneous and mesenteric tissue but to little or no degree in deposits adjacent to the kidneys and sex glands after 80 to 106 days of intensive tocopherol therapy.

The effect of thiamine-free, high-protein diets on rats. W. J. DANN. *Dept. of Physiology, Duke Univ. School of Medicine, Durham, N. C.* Banerji (Biochem. J. 35: 1354; 36: 530.) maintained rats for 3 to 4 months on thiamine-free diets containing 80% of casein; they grew moderately well, showed no polyneuritis or bradycardia, but excreted increased amounts of bisulfite-binding substances (BBS), and their kidney tissue exhibited the catatoculin effect.

These observations have been extended by maintaining albino rats of the Vanderbilt strain for more than a year on a diet of Labco cascins 80%, peanut oil 15%, salts 5% with added choline chloride, riboflavin, pantothenic acid, pyridoxine, and vitamins A, D, and E. Ten four-week-old rats were given this diet, and three died after 168, 263, and 336 days respectively; seven were killed

from day 384 to 470. Mortality was similar among other groups given this diet plus thiamine, whether the rats were pair-fed or fed *ad lib.* The most common cause of death was inanition following formation of hairballs in the stomach; a number of the rats killed also had hairballs. The incidence appeared greatest among the control rats fed *ad lib.*

After one year on the diet, surviving rats receiving no thiamine excreted more BBS than controls, had a mean heart rate of 400 against 475 for controls, weighed 176 gm. compared with 173 gm. for pair-fed controls and 259 gm. for controls fed *ad lib.* Controls fed *ad lib* had rough coats compared with glossy ones in the other groups. Aside from stunting, the rats receiving no thiamine appeared in excellent condition.

The excretion of riboflavin by young women on several levels of intake. MARGARET DAVIS and HELEN OLDFHAM (introduced by Thelma Porter). *Dept. of Home Economics, Univ. of Chicago, Chicago, Ill.* Riboflavin excretion of young women on a diet in which the amount of the vitamin was progressively increased was followed over a period of eight months.

Average daily riboflavin intakes during Periods I and II were 0.29 and 0.28 mg./1000 calories respectively. Dietary changes brought intakes to 0.49 and 0.66 mg./1000 calories during Periods III and IV. Total daily intakes averaged 7.1 mg. during Period V, which lasted two weeks. Intake during Period VI was 0.63 mg./1000 calories. From five to nine subjects were studied on each level.

Physical examinations at the beginning of the experiment and following Periods I and II revealed no signs of riboflavin deficiency.

Preliminary observations, with the subjects on their usual diets, showed an average daily urinary excretion of 435 mcg. Excretions "levelled off" within a week after each change in diet. Daily excretions during the first four periods averaged 119, 107, 150, and 263 mcg. respectively. Excretions rose sharply during Period V, but after two weeks on a lower intake, the average was 325 mcg.

During the preliminary study, average return of a 1-mg. test dose was 16%. At the end of the first two periods returns averaged 2.8 and 4.5%. With increased intake the return was 11.8% at the end of Period III, and 16.3%, equalling the preliminary level, at the end of Period IV. Returns were not increased by supplementation, the average at the end of Period VI being 15.6%.

Although levels of fecal excretion differed considerably among individuals, the amount excreted by each person remained relatively constant despite dietary variations. Daily excretions at the end of the first four periods averaged 686, 496, 575, and 580 mcg. respectively. At the end of Period VI excretions averaged 599 mcg.

The nutritive value of Michigan fish. I. The

nicotinic acid content of lake herring, carp, common suckers and burbot. JESSIE L. FINLEY (by invitation), THELMA PORTER, P. I. TACK (by invitation), EDNA LEFFLER (by invitation), NORMA SCOTT (by invitation) and RUTH NITCHALS (by invitation). *Dcpt. of Foods and Nutrition, School of Home Economics, Michigan State College, East Lansing.* Freezing, smoking, baking and seasonal and environmental conditions have been studied as they affect nicotinic acid content of lake herring (*Leucichthys artedi*), common suckers (*Cotostomus c. commersonii*), carp (*Cyprinus carpio*), and burbot (*Lota lota maculosa*). The tissue was digested with enzyme (polidase-S) in a solution at pH 7 for 16-18 hours at 45°C. A modification of Dann and Handler cyanogen bromide colorimetric method was used.

Series of lake herring from Saginaw Bay averaged 55, 31 and 23 meg. of nicotinic acid per gram of edible tissue; herring from Green Bay contained 27 and 23 meg. per gram. The significant difference is believed due to season and environment. Series of common suckers averaged 13 and 11 meg. of nicotinic acid per gram of tissue, carp 15 meg. and burbot 16 meg.

Freezing and subsequent storage of filleted fish caused insignificant loss of nicotinic acid in carp, common sucker and lake herring. Baking losses were insignificant in 4 series of fresh or frozen fish. Smoked herring retained an average of 66 per cent of the nicotinic acid in the unprocessed tissue. Two series of common suckers retained 55 and 89 per cent; the higher retention was in the series cured for a shorter period in a brine of lower salt concentration.

An average serving of the lake fish observed in this study would furnish approximately  $\frac{1}{5}$  of the daily nicotinic acid requirement of an average man.

**Nutrition studies in the New Orleans area.** GRACE A. GOLDSMITH. *Dept. of Medicine, Tulane Univ., School of Medicine, New Orleans, La.* Dietary surveys have been conducted in Louisiana recently by several investigators, a total of 6,708 grade and high school students and 1862 families being studied. The diets of 8 to 75% of persons in the various groups were found to be inadequate, while only 0.3 to 41% of the diets satisfied National Research Council recommendations. The diets were often low in minerals, vitamins of the B complex, ascorbic acid and vitamin A. Medical examination, by the State Health Department, of 545 school children included in these surveys showed 44% to be undernourished, and 10.8% to be anemic.

Another group of 688 children were examined specifically for evidence of nutritional deficiency. There was a high incidence of dental defects, old rickets, and findings suggestive of riboflavin, niacin, vitamin A, and ascorbic acid deficiency.

Of 200 patients examined in medical wards of Charity Hospital more than 40% had findings suggestive of riboflavin and/or niacin deficiency while signs suggestive of thiamine and vitamin A deficiency were frequently encountered. Plasma ascorbic acid was low in two-thirds of a group of patients studied in a medical clinic. These findings were corroborated by ascorbic acid "load" (tolerance) tests. The excretion of niacin derivatives in the urine was low in a large percentage of hospitalized patients studied.

The dietary records and the urinary excretion of thiamine, riboflavin and F<sub>2</sub> have been examined in a group of pregnant women attending prenatal clinics of the State Health Department. Findings will be discussed.

**The influence of carbohydrates on in vivo tooth decalcification in rats by acid beverages.** ROSS A. GORTNER, JR. (by invitation), J. S. RESTARSKI (by invitation) and C. M. McCAY. *Naval Medical Research Inst., National Naval Medical Center, Bethesda, Md.* Ingestion of 20 cc. daily of a common soft drink for one week causes gross destruction of enamel on rat molars. Analyses show this beverage to contain 10 per cent sucrose and 0.055 per cent phosphoric acid, with a pH of 2.6.

When the sucrose is replaced by saccharin to give a solution of the same pH and sweetness, very little tooth decalcification results. Although a sucrose solution alone has no effect on the enamel surface, the presence of sucrose in the acid drink greatly exaggerates the destructive effect of the acid. Comparable results have been obtained using maltose and glucose, but preliminary studies with a few rats suggest that lactose does not have this synergistic action with acid.

The possibility that the greater viscosity of the sucrose-acid solution, as compared with the saccharin-acid solution, was mainly responsible for the strikingly different effects of these beverages, has been investigated. By adding physiologically inert dimethoxycellulose (methocel) to the saccharin-acid solution, the viscosity was increased to that of the sucrose-acid solution without materially increasing the decalcifying properties of the beverage over that of the saccharin-acid alone.

Analyses of complete sets of molars from 50-55 day old rats have shown the normal enamel content to be around 16 per cent. Rats that drink the saccharin-acid solution for one week have about the same percentage of enamel; however, ingestion of the sucrose-acid drink for a comparable period lowers the enamel content of the molars about 25 per cent.

**Further observations on experimental dietary**

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<sup>1</sup> The opinions and views set forth in this abstract are those of the writers and are not to be considered as reflecting the policies of the Navy Department.

**hepatic injury.** PAUL GRÖGÖRY and HARRY GOLDBLATT (by invitation). *Dept. of Pediatrics, School of Medicine, Univ. of Pennsylvania and Dept. of Pathology, School of Medicine, Western Reserve Univ.* The quantity of the peculiar pigment ("carotene"), to be found in dietary liver cirrhosis, in the rat, is appreciably decreased when diets are used free from cod liver oil. Inactivation of estrogenic hormones by normal liver is interrupted in rats suffering from dietary liver cirrhosis. This reaction can be followed through vaginal smears in castrated rats kept on a cirrhosis producing diet and whose spleens have been implanted with small pellets of crystalline estrogenic hormone. Methionine (50 mg. daily) or cascain-hydrolysate (1 gram daily) used as supplements have proved to be potent therapeutic factors in restoring the normal inactivating ability of the liver cells with regard to estrogenic hormone. Variations in measured food intake have shown no correlation with these therapeutic results. Pellets of estrogenic hormone in the spleen exert a definite protective effect on the liver: a smaller percentage of rats develops liver cirrhosis and then in a milder form than control castrated or normal animals without such implanted hormone pellets. It is especially significant that this protection of the liver is independent of the estrogenic effect of estrone and is probably linked with its anabolic, N-sparing (local hepatic?) effect.

**The stabilization of carotene in linoleic acid by tocopherol and rice bran extract.** PAUL GRÖGÖRY and R. M. TOMARELLI (by invitation). *Dept. of Pediatrics, Univ. of Pennsylvania, School of Medicine and Wyeth Inst. of Applied Biochemistry, Philadelphia.* Earlier experiments demonstrated that rice bran extract acts synergistically with "butter yellow" in the retardation of the oxidation of linoleic acid. In the present nutritional study rice bran extract was again shown to participate in an antioxidant synergism; in this case it enhanced the activity of tocopherol in the preservation of carotene dissolved in linoleic acid both "in vivo" and "in vitro". Vitamin A depleted rats failed to grow and soon died when supplemented daily with 3.5 gamma of carotene in 0.1 ml. of linoleic acid given by mouth. Simultaneous administration of 0.2 ml. of rice bran extract was ineffectual. 2 mg. of mixed tocopherol with the same carotene supplement permitted fair growth. When 0.2 ml. of rice bran extract is added to tocopherol and carotene, a significantly better growth was obtained. That this difference was caused by better utilization of carotene could be proven by showing that the weight curves of the two groups soon became identical when rats from each group received an excess of carotene in cottonseed oil. The enhancement of the antioxidant activity of tocopherol by rice bran extract could

also be demonstrated "in vitro". With the same proportion of carotene, tocopherol, linoleic acid and rice bran extract as in the feeding experiments, at room temperature, the presence of rice bran extract increased the preservation time of carotene four fold. A chemical study was made of the relationship of carotene and tocopherol disappearance to peroxide number increase with and without the presence of rice bran extract.

**Chronic thiamin deficiency.** WILLIAMINA A. HIMWICH (by invitation) and HAROLD E. HIMWICH. *Dept. of Physiology and Pharmacology, Albany Medical College, Union Univ., Albany, N. Y.* The value of the fasting blood level of pyruvic acid in detecting chronic thiamin deficiency has recently been assailed. Six dogs were maintained on a thiamin-free diet supplemented with just sufficient thiamin to prevent the appearance of deficiency symptoms for periods of 4-8 weeks. Upon the development of symptoms 5 mg. of thiamin were given orally and a chronic deficiency again allowed to develop. The study continued for approximately 18 months. Pyruvic acid tolerance and glucose tolerance tests were made upon each dog at different stages of chronic deficiency, after a period of adequate feeding of thiamin and in acute thiamin deficiency. Fasting blood samples were drawn twice weekly from the time of the administration of one 5 mg. dose of thiamin to a second dose. Three dogs, used as controls were given optimum amounts of thiamin. Pyruvic acid, lactic acid and glucose determinations were made on all blood samples.

The glucose tolerance tests proved a better measure of the progress of the deficiency than did the pyruvic acid tolerance tests. Although all the pyruvic acid values in any one glucose tolerance test gave a consistent view of the degree of deficiency almost as much information was gained from the initial value. As long as the dog ingested his daily ration of food, the fasting pyruvic acid level was the best single measure of the progress of the developing deficiency. (Aided by a grant from the Williams-Waterman Fund of the Research Corporation.)

**Vascularization of the cornea as a result of lysine deficiency.** CHARLES W. HOCK, W. KNOWLTON HALL, EDGAR R. PUND (all by invitation) and V. P. SYDENSTRICKER. *Depts. of Medicine, Biochemistry and Pathology, Univ. of Georgia School of Medicine, Augusta.* Young albino rats were placed on a lysine deficient diet at weaning in order to investigate the development of corneal vessels as described by Totter and Day. The protein of the diet was either from rolled oats, or with most of the rats, zein supplemented with amino acids so that, with lysine, normal growth resulted. In the absence of lysine, corneal vessels observable by biomicroscopy appeared in from five days to two months. The first definite change seen, usually,

was edema of the conjunctiva followed by congestion with engorgement of the limbic circumferential vessels from which newly formed capillaries soon appeared at irregular intervals. These eventually reached the center of the cornea where they anastomosed with capillaries from the opposite side. The feeding of lysine produced narrowing of the corneal capillaries until they could no longer be seen with the slit-lamp.

Histological sections of eyes from ten rats confirmed the slit-lamp observations. Corneal capillaries were noted in two instances before they were demonstrable by the slit-lamp, though in one of these, streaks had been seen. In four instances where rats had been fed lysine until the capillaries could no longer be seen with the slit-lamp, minute vessels were observed histologically.

The capillaries grew in buds from the subepithelial limbic vessels and extended throughout the cornea immediately beneath the basement membrane of the overlying epithelium and thus produced ridges. (Aided by grants from The John and Mary R. Markle Foundation and Merck and Co.)

**The effect of tocopherol on essential fatty acid utilization.** E. L. HOVE and PHILIP L. HARRIS (introduced by John R. Murlin). *Research Labs., Distillation Products, Inc., Rochester 13, N. Y.* Tocopherols greatly increase the effectiveness of methyl linolate in curing essential fatty acid deficiencies in rats. This action is evident at linolate levels below 80 mg. per day. Doses of natural a-tocopherol between 0.25 and 1.0 mg. per day are equally effective. The synergy between tocopherol and linolate is also evident when sesame oil is used as the source of linolate. When tocopherol, but no essential fat, is fed to essential fatty acid deficient rats the severity of the deficiency appears to be increased in some respects.

Quantitative estimations of water consumption, hind paw scaliness, caudal lesions, and growth were used as the criteria for the rate of cure of the essential fatty acid deficient syndrome. Iodine values and saponification numbers of the body fats were determined.

When tocopherol is fed to weanling rats on the fat free diet the development of the essential fatty acid deficiency is delayed. This offers some evidence that the synergy between tocopherol and linolate is not restricted to the gastrointestinal tract.

**The comparative growth-promoting value of the proteins of wheat germ, corn germ, and of some other protein foods of plant and animal origin.** D. BREESE JONES and KATHERINE D. WIDNESS (by invitation). *Bureau of Human Nutrition and Home Economics, Agricultural Research Administration, U. S. Dept. of Agriculture, Washington, D. C.* Defatted and processed wheat

and corn germs were fed as the sole source of protein to weanling rats at 10, 15, and 17.5 per cent protein levels in diets approximately isocaloric and nutritionally adequate with respect to dietary factors other than protein. For comparison, experiments were similarly conducted with soybean, peanut, and cottonseed flours, skim milk powder and dried whole eggs. Both the *ad libitum* and paired feeding methods were used and the results were evaluated on the basis of net weight increases and gains per gram of protein consumed over six-week periods.

Consistently higher nutritional values were found for wheat germ than for corn germ by both methods of feeding. Values for corn germ ranged from 76 to 88 per cent of those found for wheat germ. Definitely higher values at the different protein levels were obtained with egg powder than with any of the other materials fed. At 10 per cent protein level wheat germ proved as efficient as skim milk powder, but at the two higher levels the latter gave significantly higher values.

Corn germ fed at 10 and 15 per cent protein levels produced equal or greater net weight gains than were obtained with peanut or soybean flour, but it was not as effective as cottonseed flour fed at 15 and 17.5 per cent levels.

**Experimental rickets in the hamster.** JAMES H. JONES. *Dept of Physiological Chemistry, School of Medicine, Univ. of Pennsylvania, Philadelphia.* Thirty-seven hamsters at about 25 days of age were divided into 3 groups. Group I (13 animals) was given a synthetic diet low in phosphorus and no vitamin D. Group II (12 animals) was given the same diet plus phosphorus and no vitamin D and Group III (12 animals) was given the same diet with phosphorus and vitamin D. At the end of five weeks the animals were anesthetized and bled. Inorganic phosphorus was determined on the serum of each individual animal and calcium on the pooled sera of several animals. A radius of each animal was examined by the "line test" technique, and the percentage of ash was determined on the right, fat-free femur. The average serum calcium, serum phosphorus and bone ash for each group were as follows: Group I 12.7 mg. %, 2.2 mg. %, and 30.4%; Group II 11.6 mg. %, 6.3 mg. %, and 57.2%; Group III 12.1 mg. %, 5.8 mg. % and 56.2%.

The animals of Group I showed a very wide uncalcified area at the distal ends of the radii. Whereas calcification, as judged by this criterion, was apparently normal in both Groups II and III. There was no detectable difference in any respect between the latter two groups. We may conclude that it is possible to produce marked rickets in the hamster, but as with the rat, the diet must be low in phosphorus as well as being deficient in vitamin D.

Some observations on nutritional effects of choline and related compounds. T. H. JUKES, A. C. DORNBUSH (by invitation) and J. J. OLESON (by invitation). *Lederle Laboratories, Pearl River, N. Y.* The rat appears to utilize aminoethanol as a "methyl acceptor", together with such "methyl donors" as methionine or betaine, in the formation of choline. The chick appears to be unable to form choline by this means. However, chicks were found to use dimethylaminoethanol as a substitute for choline in a diet which was deficient in choline but which contained methionine. Monomethylaminoethanol was somewhat effective, but seemed to be less effective than dimethylaminoethanol. Dimethylaminoethanol did not promote growth of chicks on a basal diet deficient in methionine, but growth was greatly stimulated when dimethylaminoethanol and methionine were both added to this diet.

Growth of the "cholineless" mutant (No. 34486) of *Neurospora crassa* was stimulated by dimethylaminoethanol which appeared to be as effective as choline chloride on a molar basis. The activity of monomethylaminoethanol varied from 8 per cent (at low levels) to 40 per cent (at high levels) of the activity of dimethylaminoethanol.

A sample of crude aqueous liver extract was submitted to hydrolysis with barium hydroxide followed by precipitation with reineckeate. The filtrate was tested with the cholineless mutant, and was found to be active.

The hypothesis may be considered that aminoethanol might be transformed to choline in three successive steps each of which consists of the addition of a methyl group. The rat presumably may carry out all three steps, while the chick and the cholineless mutant (No. 34486) of *Neurospora* appear to carry out the third step, and possibly the second step, but not the first step.

The lipid partition of isolated cell nuclei of dog and rat livers.<sup>1</sup> MILDRED KAUCHER, ELSIE Z. MOYER, ALLEN J. RICHARDS (all by invitation) and HAROLD H. WILLIAMS. *Research Lab., Children's Fund of Michigan.* Lipids are essential cellular components and are known to be especially important in the structure of cell membranes. The lipid partition has been determined for cryochem dried nuclei, isolated according to the procedure of Dounce [J. Biol. Chem. 147: 685 (1943)] and for comparable samples of whole liver tissue of normal dogs and rats and rats treated with butter yellow (p-dimethylamino-azobenzene).

The total lipid contents of the nuclei were 16.5 and 18.1 per cent, respectively, for the dog and rat livers, compared to 17.2 and 14.9 per cent for the whole tissue. Qualitatively, the lipid partition

was similar, but the phospholipid which comprises over half of the total lipid was significantly higher in the nuclei than in the whole liver tissue. The major portion of the phospholipid was choline-containing, mainly lecithin. No significant amounts of cerebrosides could be detected.

Isolated cell nuclei from the livers of rats receiving butter yellow contained significantly less phospholipid and more free and combined cholesterol than nuclei from the livers of normal rats.

Effect of storage on thiamine, riboflavin and niacin in rice. M. C. KIK. *Univ. of Arkansas, College of Agriculture, Fayetteville.* Samples of rice and its by-products of three varieties, Supreme Blue Rose, Early Prolific and Fortuna were stored for 2½ years at room temperature in dark brown bottles. The average thiamine, riboflavin and niacin losses in three samples (whole and ground kernels) are given below. The samples of bran and polish molded considerably which may account for the high losses.

	Whole kernels, loss (per cent)			Ground kernels, loss (per cent)		
	Thiamine	Riboflavin	Niacin	Thiamine	Riboflavin	Niacin
Rough...	10.87	6.34	4.12	22.10	8.75	5.76
Brown...	25.40	4.20	3.87	29.00	7.57	6.80
White...	29.40	5.44	3.77	34.50	6.40	5.71
Bran...	50.37	16.35	15.20			
Polish...	45.30	18.00	14.60			

Similar samples of two varieties Lady Wright and Improved Blue Rose were placed for 2½ years in freezer-storage locker (temperature 14°F.). No significant losses of thiamine or niacin and only slight losses of riboflavin occurred during cold storage. The average losses for this set are given below.

	Loss (per cent)		
	Thiamine	Riboflavin	Niacin
Rough.....	1.81	1.98	1.10
Brown....	1.21	3.84	1.95
White....	0.94	1.61	1.20
Bran....	0.40	1.73	1.25
Polish....	0.16	1.75	1.61

Rice samples (whole kernels) in various stages of milling were stored in glass containers in the light at room temperature (average 84°F.). Ground kernels were stored in paper bags in t room temperature. The average per are given below. These samples thiamine.

<sup>1</sup> Dr. George R. Sharpless, Henry Ford Hospital, supplied the dog liver and butter yellow-treated rat livers.

	After 3 months, loss (per cent)	After 9 months, loss (per cent)	
		Ground kernels	Whole kernels
Rough.....	5.01	12.73	8.24
Brown.....	4.75	11.28	11.43
Undermilled.....	5.40	14.67	7.18
Milled.....	7.38	15.35	13.19

Losses up to 7 per cent were found after 3 months storage in ground kernels, and up to 15 per cent in ground kernels and 13 per cent in whole kernels after 9 months storage. The losses were slightly lower for whole kernels than for ground kernels. (Aided by a grant from the Williams-Waterman Fund of Research Corporation.)

**Effects of pre-flight and in-flight meals of varying composition upon altitude tolerance.** C. G. KING and (by invitation), H. A. BICKERMAN, W. BOUVET, C. J. HARRER, J. R. OYLER and C. P. SEITZ. *Dept. of Chemistry, Columbia Univ.* The investigation was undertaken to explore certain practical feeding practices that might have a significant bearing upon altitude tolerance. Primary emphasis was placed upon quantitative records of performance, food intake, and standardization of human test subjects. Inanition (beyond 4 hours) was least favorable at all elevations (2,000 to 17,000 ft.); high protein meals were next, and high carbohydrate meals providing 800 to 1000 calories were most favorable. Fats were intermediate. Moderate variation in vitamin intake and acid-base balance appeared to be of lesser importance but of some significance.

Citric acid excretion was doubled by four exposures of three hours each per week, at 17,000 ft. Peripheral vision (cortico-retinal function) and block placement (psychomotor function) tests gave consistent data in repeated measurements impairment at altitude.

**Deficiency of rate of energy conversion (power) in starvation.** MAX KLEIBER. *College of Agriculture, Univ. of California, Davis.* A group of 11 rats, kept at 20-24°C, and receiving only water, survived on the average 9.4 days. A corresponding group, with access to minerals and vitamins besides water, survived 9.0 days. A third group, receiving daily 1.5 g. casein in addition to vitamins, minerals and water, had a mean survival time of 11.5 days. A fourth group, with 1.9 g. glucose instead of the casein, lived on the average 10.5 days; and a fifth group, with only water and .19 g. glucose, died on the average after 13.2 days.

The relation of energy requirement and survival time in starvation was tested further with rats starving at two different levels of environmental temperature. Thirteen rats starving at 20 to 24°C survived on the average  $9.0 \pm 0.7$  days, whereas

21 rats, starving in an environment of 30°C had a mean survival time of  $17.2 \pm 1.5$  days.

For the rats starved at 20-24°C the second but last day's metabolic rate (measured at 30°C) averaged  $53.8 \pm 2.7$  per cent of the standard metabolic rate after 16 hours fast. The corresponding figure for the rats starved at 30°C is  $33.1 \pm 2.2$  per cent.

This highly significant difference in the metabolic rate before death, dependent on the environmental temperature, supports the idea that the major factor in death from complete starvation is a deficiency in power, that is rate of energy conversion, which may occur when the animal body still contains a considerable amount of chemical energy.

**A nicotinic acid deficiency in the rat caused by feeding corn.** WILLARD A. KREHL (by invitation), LESTER TEPLEY (by invitation) and C. A. ELVEHJEM. *Dept. of Biochemistry, Univ. of Wisconsin, Madison.* Since the time of Casal, corn has been indicated as a causative factor in pellagra, and Aykroyd has suggested that more nicotinic acid is required to prevent this disease when corn is the chief dietary component. These views concerning corn have been examined experimentally by feeding rats a highly purified synthetic ration (essentially free of nicotinic acid) supplemented with either yellow corn, white corn, or corn grits at a level of 40 per cent of the entire ration. In all cases, the rations containing corn produced a nicotinic acid deficiency in the rat, characterized by a severe growth depression which was completely counteracted by nicotinic acid. Graded amounts of nicotinic acid, up to 1.5 mg. per 100 g. of ration, resulted in corresponding increments in growth. Trigonelline and a specially prepared "nitro-elluate" preparation, fed at levels up to the equivalent of 23 ug. of B<sub>6</sub> per 100 g. of ration, were ineffective in counteracting the deficiency.

The effect caused by corn is apparently not related directly to its nicotinic acid content since polished rice and rolled oats, which contain less nicotinic acid than yellow corn produced no growth depression when fed under identical conditions. Although nicotinic acid *per se* has been most effective in counteracting the effect of corn, there are indications that intestinal synthesis may play an important rôle, since carbohydrates other than sucrose modify the growth depression caused by corn and furthermore, small supplements of milk, supplying very small amounts of nicotinic acid, affords a marked but latent protection.

**The influence of fluoride on in vivo tooth decalcification in rats and dogs by acid beverages.**<sup>1</sup> C. M. McCAY, ROSS A. GORTNER, JR. (by invitation)

<sup>1</sup> The opinions and views set forth in this abstract are those of the writers and are not to be considered as reflecting the policies of the Navy Department.

tion) and J. S. RESTARSKI (by invitation). *Naval Medical Research Inst., National Naval Medical Center, Bethesda, Md.* White rats allowed to ingest 20 cc. daily of a common soft drink containing 10 per cent sucrose and 0.055 per cent phosphoric acid, and having a pH of 2.6, exhibit gross destruction of the enamel on the molars within one week; using a prepared solution of the same sugar and acid concentration as the commercial beverage, similar results have been obtained. The greatest decalcification occurs on the lingual surface and no destruction takes place below the gingival margin, indicating that the action is direct rather than systemic.

Comparable studies with young dogs receiving 500 cc. daily of the sweetened acid solutions show that their deciduous teeth are similarly attacked.

The inclusion of from 1 to 20 ppm. F (as sodium fluoride) in the sucrose-acid solution effectively decreases, but does not prevent completely, the destruction of enamel in most of the animals studied. Within the limits tested, no differences have been noted in the protective action of different levels of fluorine. All evidence suggests that the fluorine acts directly on the enamel surface as the solution comes in contact with the teeth, possibly by the formation of highly insoluble fluorapatite or calcium fluoride. Photomicrographs of the enamel surfaces show that in the presence of fluorine both the enamel rods and interprismatic substance are less affected by the acid.

**The necessity of fluorine in the diet. II.** J. F. McCLENDON and WM. C. FOSTER (by invitation). *Hahnemann Medical College, Philadelphia, and the Experimental Farm of J. F. McClendon.* It was previously reported (Fed. Proc. 3:94, 1944) that rats (whose mother was on a low fluorine diet) lost practically all the crowns of the first and second molar teeth in 48 and 70 days, on a fluorine-free diet. We repeated this experiment on rats whose mother was on a high fluorine diet. After 56-70 days on the fluorine-free diet all molar teeth were carious but the caries were not so extensive as in the previous experiment. This indicates that the fluorine content of the teeth at weaning reduces the rate of decay but not the initiation of caries. This fluorine-free diet was prepared from crops raised by hydroponics: corn 16, corn sugar 30, corn oil 16, yeast 16, sunflower seeds 16, soy beans 4, calcium citrate 1 and NaCl 1. Litter-mate controls, 70 days on a diet of the same composition of crops raised in soil, showed caries in only one third the molar teeth and the caries were not as large as those in rats on the fluorine-free diet. The growth rate of 125 rats receiving sodium fluoride or fluorapatite (in addition to the low fluorine diet) averaged 15% higher than that of litter-mate controls. Rats fed fluorapatite (2 males, 5 females) bore and reared 4 litters in 6 months whereas the litter-mate controls on same low fluorine diet alone (3

males, 5 females) had no litters. (Aided by the Aluminum Co. of America).

**Significance of diet in familial periodic paralysis. IRVINE MCQUARRIE and MILDRED R. ZIEGLER (by invitation). Dept. of Pediatrics, Univ. of Minnesota, Minneapolis.** Because ingestion of glucose tends to provoke and potassium salts to relieve attacks of flaccid paralysis in persons afflicted with this bizarre hereditary disorder, an attempt was made to ascertain the definitive rôle of diet in the genesis of spontaneously occurring paralytic episodes. A series of widely differing diets were given in succession to a 15 year old victim of the disease. With the free carbohydrate content ranging between 5 and 378 gm. and the potassium between 0.5 and 14.0 gm daily, it was found that the ratio between the two (CH/K) was much more important than the absolute amount of either constituent. With the patient on ordinary mixed diets with restricted carbohydrate (75 to 285 gm. daily) or on whole milk diets with added sugar, critical ratios ranged between 68 and 55. Further increases in the amount of carbohydrate were found to lower the critical ratio. On high protein diets (3 gm./kg.) no attacks occurred, despite reduction in K intake to 0.5 or 1.0 gram daily, until the CH/K was increased to 70. High fat (ketogenic) diets were found to favor occurrence of attacks, even when the free-CH/K was as low as 10. When the calculated "total available glucose" of the diets was used for the ratio instead of preformed carbohydrate, the contrast between the effects of the last two diets was equally striking. Fasting caused temporary cessation of attacks. Increasing the water or NaCl intake had very little effect on genesis of paralytic attacks.

**Studies on forced feeding after burns.<sup>1</sup>** FRIEDA L. MEYER, WILLIAM E. ABBOTT and JOHN W. HIRSCHFIELD (introduced by Arthur H. Smith). *Depts. of Surgery and of Physiological Chemistry, Wayne Univ. College of Medicine, Detroit.* It has been demonstrated in patients and under more strictly controlled conditions in animals that a negative nitrogen balance exists after burns. Forced feeding in patients improved the state of nitrogen balance but the clinical condition was very poor. The same undesirable effects were produced in two dogs force-fed a diet three times their control diet in protein content and twice the caloric value. The animals' condition was such that one animal was sacrificed on the 6th day, and the other on the 12th day post-burn. Blood studies showed a greater increase in plasma volume and decrease in hematocrit than was found in the control animals. Both total protein and albumin concentration showed a decrease and in one dog the non-protein

<sup>1</sup> Work done under contract with the Office of Scientific Research and Development.

nitrogen was increased markedly. In an attempt to determine the cause of the undesirable effects, two dogs were fed a diet with the same nitrogen increase, but no increase in caloric value. These studies are still in progress.

**Effect of tocopherol phosphate on creatinuria in progressive muscular dystrophy.** A. T. MILHORAT. *Depts. of Medicine and Psychiatry, Cornell Univ. Medical College, The Russell Sage Inst. of Pathology and the New York Hospital.* The water soluble disodium alpha-tocopherol phosphate given orally in single doses of from 1 to 5 gm. to 7 patients with progressive muscular dystrophy was without effect on the creatinuria of any of the subjects. On the other hand, effects on creatinuria were observed in certain of these subjects when tocopherol phosphate was administered intramuscularly in single doses of from 90 to 180 mg. In 2 patients the output of creatine was unchanged; and in another the effect was questionable. In 1 subject the output of creatine was decreased from a spontaneous daily level of 700 mg. to 556 mg. for 1 day, and in another subject from 417 mg. to 350 mg. for 2 days. The amounts of reduction were at least twice as great as the maximum spontaneous variations observed during periods of control. In another patient who spontaneously excreted an average of 190 mg. creatine daily (maximum variation = 20 mg.) the daily amounts of creatine following the injection were: 165, 125, 140, 146, 125, 147, 204 mg.

The observations are of significance in relation to our recent studies on the function of the gastrointestinal tract in the utilization of tocopherol and on the nature of the defect of this function in progressive muscular dystrophy.

**Some studies on the microbiological method of vitamin determination.** MAVIS C. NYMON and WILLIS A. GORTNER (introduced by L. A. Maynard). *School of Nutrition, Cornell Univ., Ithaca, N. Y.* These studies were undertaken to simplify and increase the reliability of the microbiological determination of vitamins.

Replacing cotton plugs with glass burette caps for the assay tubes was found to be very satisfactory. Identical results were obtained when the assay tubes were autoclaved 15 minutes at 15 pounds. This eliminates preparation of cotton plugs and at the same time prevents any stimulatory or inhibitory effect on the assay organism that may be caused by particles of cotton (Sherwood and Singer, *J. Biol. Chem.* 155: 361, 1944).

Experience in this laboratory and others has shown that when cultures of *Lactobacillus arabinosus* 17-5 and *L. casei* ε are transferred to yeast glucose agar stabs at monthly intervals according to the recommendations of Snell and Wright (*J. Biol. Chem.* 139: 675, 1941) there is a gradual departure in linearity of response to added niacin or riboflavin. By weekly transfer through nutrient-

rich broth to liver tryptone agar such degenerated cultures were improved greatly. For a *L. arabinosus* 17-5 culture, for example, the maximum point of linear response was increased from 0.15 to over 0.4 micrograms of niacin.

As a means of securing greater reproducibility of standard curves, of obviating the frequent transfer of the culture organisms, and at the same time maintaining highly viable cultures, a simple lyophilic procedure was applied to cultures of *L. arabinosus* 17-5 and *L. casei* ε. The results of storage thus far have indicated that after three months' storage at room temperature these cultures are fully as viable as the cultures carried by frequent transfer. Since these cultures are completely desiccated and are sealed under high vacuum they presumably will maintain this activity for a much longer period. It should be feasible to lyophilize a 6 months' or year's supply of cultures at one time. Further studies on this phase are being carried out. (Aided by a grant from the Consolidated Edison Co. of New York, Inc.)

**The inability of human or beef globin to support normal hemopoiesis in the rat without added isoleucine.** J. M. ORTEN, A. U. ORTEN (by invitation) and J. E. BOURQUE (by invitation). *Dept. of Physiological Chemistry, Wayne Univ. College of Medicine, Detroit.* Previous work in this laboratory has demonstrated that dried beef blood fed to rats as the source of protein fails to support normal growth and hemoglobin formation. The present study was made to ascertain the growth and hemopoietic value of purified globin from human or beef blood.

The globin preparations were incorporated in a synthetic diet at a 19.6 per cent level and fed to weanling rats. Complete vitamin supplements were supplied separately. Control animals were fed the same diet excepting that casein was used as the protein.

Animals fed either human or beef globin failed to grow and within 4 weeks developed an anemia. All rats died within 6 weeks. Control rats remained normal in all respects.

At this time, reports indicated that isoleucine is present in hemoglobin in small amounts. Therefore, anemic rats fed human or beef globin for 4 weeks were given 100 mg. dl-isoleucine daily as a supplement. Their food intake was restricted to the average daily amount ingested prior to supplementation, to prevent an increase in food consumption which would have introduced a second variable.

Every rat showed a steady rise in hemoglobin to normal values within 4 weeks; these were maintained during a six-week period of supplementation.

Isoleucine supplementation was then discontinued and again an anemia developed and the animals died.

These observations indicate that isoleucine, al-

though present in a relatively small amount in the hemoglobin molecule, is essential for normal hemopoiesis.

**Excretion of orally administered B-vitamins in health and disease.** W. A. PERLZWEIG, J. M. RUFFIN (by invitation) and D. CATER (by invitation). *Depts. of Biochemistry and Medicine, Duke University, Durham, N. C.* Oral doses of 5 mg. thiamine, 5 mg. riboflavin and 50 mg. nicotinamide were given to 69 well fed, normal subjects, 85 ambulatory dispensary patients and 69 hospitalized public ward patients. The patients were taken at random on admission. The urinary excretion of these vitamins in 2 hours was determined. The data are summarized in the table and their significance will be discussed. The incidence of low excretion values among patients presenting a variety of diseases was considerably greater than in the normal subjects. (This work was done in part under a contract with the Office of Scientific Research and Development; it was also aided by the Nutrition Foundation, the John and Mary R. Markle Foundation and the Duke University Research Council.)

#### 2 HOURS' EXCRETION TEST

Lowest normal decile

Subjects	No.	Range	Mean	S.D.	Range	No.	%
Thiamine (5 mg.)							
Normals....	69	51-360	146 ± 62	0-70	7	10	
Dispens....	85	9-304	129 ± 64	0-70	17	20	
Ward.....	69	4-216	56 ± 44	0-70	51	71	
Riboflavin (5 mg.)							
Normals....	69	275-3510	1376 ± 620	0-500	7	10	
Dispens....	82	78-2240	1035 ± 568	0-500	27	31	
Ward.....	69	22-1760	712 ± 502	0-500	30	43	
Niacin, F <sub>2</sub> (50 mg. amide)							
		mg.	mg.	mg.			
Normals....	69	1.9-8.5	5.0 ± 1.5	0-2.8	7	10	
Dispens....	73	0.8-7.9	3.8 ± 1.6	0-2.8	20	27	
Ward.....	69	0.5-9.0	3.4 ± 1.7	0-2.8	33	46	

**The utilization of iron from different foods by normal young rats.** ORREA F. PYE (by invitation) and GRACE MACLEOD. *Nutrition Lab., Teachers College, Columbia Univ., New York City.* Weekly hemoglobin production and iron stored during a 6-week period were studied in normal young male rats on two series of diets varied in (1) source of iron (2) quantity of iron. When diets furnished daily 0.002 mg. iron per gram of body weight from different sources, hemoglobin production and iron retention were highest and about the same on ferric chloride and whole wheat flour, and almost but not quite as high on beef liver. The iron of beef muscle, egg yolk, kale (uncooked and cooked),

and spinach (uncooked and cooked) was less well utilized; the differences among these foods were small.

In the second series four diets were used each containing one third whole milk powder plus, in Diet I, two thirds whole wheat flour; in Diet II, one third whole wheat flour and one third unenriched patent flour; in Diet III, two thirds unenriched patent flour; while Diet IV was Diet III plus ferric chloride sufficient to make the iron content equal to that of Diet I. The diets containing unenriched flour were supplemented with vitamins to keep vitamin levels equal in all diets. Hemoglobin formation and iron retention were higher than in the first series on Diets I and IV on which average intake was slightly above 0.002 mg. iron per gram of body weight daily. On Diet II, daily iron intake averaging below 0.002 mg. per gram of body weight, hemoglobin formation and iron retention were only fair; and on Diet III, intake averaging below 0.001 mg., losses in both hemoglobin level and iron content resulted.

**The vitamins required for normal reproduction in rats.** L. R. RICHARDSON and A. G. HOGAN. *Dept. of Agricultural Chemistry, Univ. of Missouri.* The ration is of the synthetic type and each 100 grams contains 2000 I. U. of vitamin A, 283 I. U. of vitamin D, 2.5 mg. of alpha tocopherol, 2.5 mg. of 2-methyl-1, 4-naphthoquinone, 1 mg. each of thiamine, riboflavin and pyridoxine, 2.0 mg. of calcium pantothenate, 200 mg. of choline, 5 mg. of niacin, 100 mg. of inositol, 50 mg. of p-aminobenzoic acid and 20 meg. of biotin. A total of 60 litters from females which received this ration has been observed. Seventy per cent of the litters and 69.7 per cent of the young were weaned. When inositol was omitted from the vitamin mixture 44.3 per cent of the young were weaned; when niacin was omitted 60.4 per cent were weaned, and when p-aminobenzoic acid was omitted 75.8 per cent were weaned. The data so far are inconclusive as to the effect of omitting 2-methyl-1, 4-naphthoquinone, choline or biotin.

The addition of 1 per cent of a fullers earth eluate of liver, which supplies vitamin B<sub>c</sub> and probably unrecognized vitamins, increased the percentage of young which was weaned to 83.4. A liver filtrate which contains only 0.3 micrograms of vitamin B<sub>c</sub> per gram is just as effective as the eluate, when supplied at a level of 5 per cent. It is concluded that an unrecognized nutrient is essential if female rats are to wean the maximum number of young.

**The effects of added vitamin A on the conjunctiva, blood level and respiratory infection absence rate.** ELIZABETH CHANT ROBERTSON and A. LLOYD MORGAN (by invitation). *Depts. of Paediatrics and Ophthalmology, Univ. of Toronto.* Twenty pupil nurses, receiving 4,000 to over 12,000 I.U. of vitamin A in their daily diet were given 50,000 I.U. more per day. Twenty controls, closely

comparable as judged by conjunctival elevations and degree of transparency of their conjunctivae on slit-lamp examination were given placebos. Most were on therapy for 2 years.

Besides a detailed examination of the conjunctivae and the surrounding tissues with the naked eye, a large drawing of the slit-lamp view of the non-movable, deep conjunctival blood vessels, which are presumably attached to the outer surface of the sclera, was made on each subject every two months. This required three-quarters of an hour for each patient. Any change in elevations, the number of the deep blood vessels and the ease with which they could be seen was observed and recorded. Even after two years' therapy it was impossible to differentiate between those receiving vitamin A therapy and the controls by slit-lamp examination. Life-size Kodachrome photographs taken every 6 months were of little value because of differences in color tone. Very little change was evident in the blood vitamin A level even after 22 months of therapy. Forty-one per cent (7 nurses) of those on therapy reported 15 respiratory infections and lost 109 days from duty because of them; sixty-five per cent of the controls (11 nurses) reported 24 respiratory infections and lost 198 days from duty.

**"Relative" thiamin tolerance in normal and cancerous individuals.** W. T. SALTER and (by invitation) R. C. ROSKELLEY. *Labs. of Pharmacology and Toxicology, Yale Univ., School of Medicine.* An excess of thiamin was administered to fasting individuals and the rate of urinary excretion determined at hourly intervals thereafter. The "PAYF" fraction described by C. P. Rhoads was also studied. The ascending limb of the excretion curve often reached a peak at three hours. Thereafter the excretion declined in approximately semi-logarithmic fashion. From such data it is possible to derive estimates of the storage-reserve of free thiamin in various individuals. The value tends to decline with advancing years. Even so, some individuals appear to be relatively less capable of maintaining a concentration of free thiamin than others. A high percentage of cancerous patients are thiamin deficient. Moreover, certain of these appear to show a relative deficiency when their tolerance to thiamin is tested.

**The effect of thyroxin on the vitamin A content of the liver of male and female albino rats.** MYRA M. SAMPSON and MARGARET S. HACKFORD (by invitation). *Smith College.* Forty-eight male and twenty-four female albino rats of the Sprague-Dawley strain, given minimum amounts of vitamin A preceding and following weaning, were transferred at the age of 26 days to individual cages and fed an adequate diet supplemented daily with 100 U.S.P. units of vitamin A. Thirty-two males and sixteen females were given daily by mouth

1/10th, 2/10ths or 3/10ths mgms. of thyroxin. The remaining sixteen males and eight females served as controls. Records were kept of the food intake and body weight of each animal. Thirty-one and fifty-two days after the beginning of the experiment rats from each group were killed and frozen immediately. Each liver was subsequently weighed, the vitamin A extracted, and the amount determined by means of the Carr-Price reaction with an Evelyn photoelectric colorimeter.

The total vitamin A content and the amount per gram of liver was greater in females than in comparable males. The vitamin A content of rats which received thyroxin was lower than that of the controls but not proportional to the amount of thyroxin administered. The decrease in vitamin A content of the liver was more pronounced in the female than in the male at the end of the periods studied. The authors conclude that rats of both sexes given thyroxin between the ages of 26 and 78 days require more vitamin A than corresponding controls and that females require more than males.

**The effect of manganese on liver tumor induction by p-dimethylaminoazobenzene.** GEORGE R. SHARPLESS. *Dept. of Laboratories, Henry Ford Hospital, Detroit.* In a study of some of the dietary factors which influence the formation of liver tumors in rats fed p-dimethylaminoazobenzene, it was observed that inclusion of the essential trace elements resulted in the appearance of tumors in a shorter time than when they were omitted from the salt mixture. Of the trace elements used (copper, manganese, cobalt, zinc, and iodine) manganese alone consistently reduced the tumor induction time. Tumors were palpable (confirmed later as hepatomas and adenocarcinomas by their rapid growth and by sections) in some animals as early as the fourteenth week, whereas littermate controls with no manganese supplement required eighteen weeks for similar development. Two diets containing respectively 6.5 and 10.5 per cent protein were used. While two per cent manganese sulfate in the first diet was toxic when fed with p-dimethylaminoazobenzene, no acute toxic symptoms were seen in animals fed the higher protein diet. The survival time was not significantly affected but the average tumor size was increased by manganese and metastases were more common.

Cirrhosis of the liver in rabbits from administration of manganese salts has been reported. In the experiments here reported no cirrhosis has been obtained in rats fed manganese without p-dimethylamino-azobenzene. However, cirrhosis in various degrees appears to precede malignant changes.

**Dental caries in the cotton rat.** JAMES H. SHAW (by invitation), B. S. SCHWEIGERT (by invitation), P. H. PHILLIPS and C. A. ELVEIJEM. *Dept. of Bio-chemistry, Univ. of Wisconsin, Madison.* The

cotton rat has been shown to be highly susceptible to the development of carious lesions. These lesions begin to develop deep in the occlusal fissures of the molars and do not become visible from the occlusal surface until fracturing of the undermined cusps occurs. An experimental period of 14 weeks after weaning was found to be optimum for observation and evaluation of the carious lesions. When a ration adequate for growth, which contained 67% fructose, glucose, sucrose, maltose or dextri-maltose was fed, a high incidence of carious lesions was observed. However if a ration was fed in which the soluble sugar was replaced completely by dextrin, the incidence of carious lesions was greatly reduced. Particle size of the ration did not appear to play any part in the production of the lesions. The addition of 43, 85 or 128 p.p.m. of fluorine as sodium fluoride to the sucrose basal ration gave progressively increasing reductions in caries incidence, however 210 p.p.m. were necessary to give the same reduction as was observed when sucrose was replaced completely by dextrin. When cotton rats were fed only mineralized milk or mineralized milk plus liver, there was a complete prevention of carious lesions. A similar effect could be produced by the isocaloric replacement of 45 parts of the sucrose in the basal ration by 20 parts of lard; however the replacement of 50 parts of the sucrose by dextrin produced only a slight reduction in the caries incidence. A definite familial variation in susceptibility to the formation of carious lesions was observed.

**Phytase activity and the availability of soybean oil meal phosphorus.** ROBERT R. SPITZER and PAUL H. PHILLIPS. *Univ. of Wisconsin, Madison.* In a study of the availability of soybean oil meal phosphorus it has been found that the phosphorus was completely available for the rat. Since it has been reported that 40 to 80% of soybean phosphorus is present in the form of phytin phosphorus and that the enzyme phytase must be present in phytin containing rations before this bound phosphorus can be utilized by the animal organism, the presence of a phytin splitting enzyme was sought.

A method for the measurement of phytase activity was developed. Since heating the entire ration at 98°C. for 48 hours had no effect on the availability of the soybean oil meal phosphorus, it is concluded that little or no phytase is present in soybean oil meal and that the availability of the phosphorus could not be attributed to the presence of this enzyme in the ration. Further investigation showed that phytase was present in the intestinal wall of the rat. Extension of these studies to other species has shown in a preliminary survey that phytase was present in the rumen and the intestinal wall of the bovine, and in the intestinal contents of the pig but not in the intestinal wall of this species.

Evidence has been obtained which indicates that the protein of soybean oil meal when fed at a 14% level and properly supplemented with vitamins or vitamin like factors was slightly superior for growth in comparison to an equivalent amount of the protein casein.

**Dried yeast as sources of protein for growth and reproduction.** BARNETT SURE. *Dept. of Agricultural Chemistry, Univ. of Arkansas, Fayetteville.* The results of three months study on a dried brewers' yeast and a dried cultured yeast as sources of protein show very good growth on 9% and excellent growth on 13% and 18% planes of protein intake without supplementation of any amino acids. To-date 12 litters of 103 young were born, averaging 8.6 young to the litter. The young born were vigorous, the majority of which had milk in their stomachs at birth. Work is proceeding on lactation.

Four more strains of cultured yeasts are being studied at 13 and 18 to 20% planes of protein intake. Excellent growth has so far been obtained during an 8 week period of study without any amino acid supplementation.

The above results indicate the possible beneficial use of certain strains of dried yeasts for human nutrition to help meet the protein shortage in Europe and Asia.

**The evaluation of the carotene content of fresh and cooked spinach.** MARION A. WHARTON (by invitation), THELMA PORTER and BERNICE BOLLINGER (by invitation). *Dept. of Foods and Nutrition, School of Home Economics, Michigan State College, East Lansing.* The National Cooperative project on the conservation of the nutritive value of foods recommended that nutritive values be expressed per gram of dry weight for both fresh and processed foods to facilitate the comparison of losses and gains from various treatments. It has been found in this laboratory and in others, that certain vegetables, after cooking, have more carotene per 100 grams dry weight than the corresponding fresh vegetables. The purpose of this study was to investigate the possible causes of this discrepancy.

Fresh spinach, purchased at the local market, was analyzed for carotene and moisture as were their corresponding samples cooked in the following ways; 400 grams in 800 ml. of boiling water (both drained on a collander and drained by suction on a Buechner funnel); small portions in cheesecloth, perforated parchment and parchment bags cooked with the large sample; and also small samples cooked in water or sealed pliofilm bags.

Carotene, calculated as mgms. per 100 grams dry weight, was 30 per cent higher in the cooked than in the raw sample but calculated on the raw weight basis, the cooked and raw values were similar. The apparent increase was due to the dif-

ference in the solid contents of the fresh and cooked products.

A linear relationship was found between the carotene content of fresh and cooked vegetables. Constants calculated on both the moist and dry weight basis permit the evaluation of the carotene content of the cooked vegetable in relation to its corresponding fresh value.

**Biological efficiency of egg proteins.** WANDA WILLMAN (by invitation), PEARL P. SWANSON, G. F. STEWART (by invitation), GLADYS T. STEVENSON (by invitation) and MIRIAM BRUSH (by invitation). *The Nutrition Lab., The Foods and Nutrition Dept., Iowa State College, Ames.* Unexpected depression in the excretion of nitrogen, creatinine, and phosphorous in the urine of rats during the period of protein-feeding in experiments designed to test the biological value of various samples of dried egg proteins have given rise to interesting speculation regarding the nature of protein metabolism and to a new viewpoint regarding the biological efficiency of egg proteins. It seems that egg proteins supply nitrogenous metabolites that are more efficiently utilized than those arising in the catabolism of body tissues coincident with existence on a protein-free diet.

The average decreases (mg. per 7-day collection period) observed in the urinary nitrogen excreted by groups of 12-15 rats following the incorporation of 3.5 per cent of protein in the nitrogen-poor diet were: fresh eggs, 65; fresh dried whole eggs, 102; dried whole eggs stored 3, 6, and 12 months, 98, 100, and 83 respectively; dried egg yolk, 102; dried egg white, 130; and nitrogen as the essential amino acids, 72. "Biological efficiencies" were, respectively: 109, 104, 112, 109, 111, 129; and 116. An equivalent quantity of pork muscle caused an increase of 34 mg. in the output of urinary nitrogen, its biological efficiency being 83. Corroborative tests studying utilization of excised rat muscle protein and rat liver protein are in progress, as are analyses of certain low-quality proteins.

The findings have been of particular significance in research going forward under the auspices of the army in the improvement of the life raft ration.

**Effect of diethyl choline on the utilization of labile methyl groups by the rat.** RICHARD J. WINZLER and VIRGINIA HARDWICK (introduced by H. J. Deuel, Jr.). *Dept. of Biochemistry, Univ. of Southern California, Medical School, Los Angeles.* In the course of studies on the ability of certain methylated compounds to act as sources for labile methyl groups, Moyer and duVigneaud (J. Biol. Chem. 143, 373 (1942)) observed that diethylmethylhydroxyethyl-ammonium chloride, the diethyl analogue of choline (diethyl choline), was highly toxic to rats on a methionine-free diet

containing homocystine. Previously Dyer (J. Biol. Chem. 124, 519 (1938)) had observed that ethionine, the ethyl analogue of methionine, was toxic to rats on a diet low in the sulfur containing amino acids. These observations prompted us to investigate the possibility that diethyl choline acts as a competitive analogue of choline, preventing the proper utilization of labile methyl groups.

Albino rats were placed on diets containing 18% arachin (a protein containing only 0.5 per cent methionine) 55% cerelose, 15% lard, 5% cod liver oil, 0.8 per cent homocystine and adequate amounts of salts and crystalline vitamins, but lacking in choline. These rats were supplemented with 25 mg. per day of choline, diethyl choline, or methionine and with various combinations of these. The growth rates were followed for two weeks and then the fat content of the livers was determined.

In agreement with Moyer and duVigneaud and with Weleh (J. Biol. Chem. 137, 173 (1941)) it was found that animals failed to grow on a low-methionine diet containing homocystine unless choline or methionine were added. Supplements of diethyl choline (25 mg./day) did not permit growth on this diet, nor did it show evidences of toxic effects either alone or with added choline or methionine.

**The occurrence of the new nutritive essential, strepogenin, in certain crystalline proteins.** D. W. WOOLLEY and HERBERT SPRINCE<sup>1</sup> (by invitation). *Labs. of the Rockefeller Inst. for Medical Research, New York, N. Y.* Strepogenin is the term used to designate an unidentified nutritive essential which has been found necessary for the growth of certain hemolytic streptococci, and for the early growth of several other species of bacteria. In the present investigations, *Lactobacillus casei* was employed as the test organism in accordance with the procedure described previously. Following earlier observations that partial hydrolysates of casein contained this factor, enzymic digests of several pure proteins have been examined for strepogenin activity. If a crude concentrate derived from liver was given a potency of 1, suitable tryptic digests of crystalline insulin had activity of approximately 40, that is, the insulin digests were about 40 times as active as the liver concentrate on a weight basis. Digests of crystalline trypsinogen showed a potency of 20, crystalline trypsin 13, crystalline chymotrypsinogen 2, crystalline chymotrypsin 16, crystalline ribonuclease 10, vitamin-free casein 5, salmine 0, egg white 0.1. The rate of liberation of strepogenin activity from these various proteins varied from one compound to another. It was most rapid in the cases of trypsinogen and trypsin, but for some of the other proteins maximal activity

<sup>1</sup> Fellow of the Nutrition Foundation.

was not attained until after about 20 hours' digestion. A method of purification of strepogenin from trypsic hydrolysates has been developed. It is

believed that strepogenin activity is associated with an intimate portion of the molecules of certain proteins.

## THE AMERICAN ASSOCIATION OF IMMUNOLOGISTS

Abstracts of papers presented for the annual meeting scheduled for Cleveland, May 8, 9, 10, 1945. On account of the cancellation of this meeting, all the papers are to be regarded as "read by title". For possible correction in any of the abstracts see the next issue.

**Studies in complement fixation. I. Malaria; the application of quantitative principles in the optimal adjustment of reagents and test conditions.** CAPTAIN SAMUEL C. BUKANTZ, Medical Corps, Army of the United States; LIEUTENANT JOHN F. KENT, Sanitary Corps, Army of the United States, and MAJOR CHARLES R. REIN, Medical Corps, Army of the United States. With the technical assistance of REBECCA GOODMAN, Division of Serology, Army Medical School Medical Center, Washington, D. C. A quantitative investigation was made of conditions resulting in maximal sensitivity and specificity of the complement fixation test with plasmoidal antigens. The 50 per cent hemolytic unit of complement was determined spectrophotometrically in the presence of the optimal concentration of amboceptor. Standard conversion factors were established which permit calculation of the 50 per cent unit with great accuracy and without constructing the curve of hemolysis.

The effect of test conditions upon reactions of serum and antigen alone and in combination was determined from alterations in the degree of partial hemolysis obtained with the 50 per cent unit of complement and multiples thereof. Refrigeration for 18 hours yielded higher degrees of specific reaction than incubation at 37°C.; complement deteriorated minimally during refrigeration and considerably at 37°C. Since the effect of antigen alone upon the activity of complement was no index of the corresponding effect in the presence of normal serum, supplementary observations made under the latter conditions were used in evaluating antigen. Non-anticomplementary concentrations of antigens were titrated to an optimum yielding maximal reactions with minimal concentrations of antibody. Human malarial sera yielded maximal reactions in final concentrations of 2 to 4 per cent depending upon the characteristics of the antigen employed. Parallel tests with these concentrations of serum and varying multiples of the complement unit showed that 3 units were optimal for the detection of minimal concentrations of antibody and anticomplementary properties of serum. A qualitative test based upon these observations is

being evaluated in sporozoite induced *P. vivax* malaria.

**The effect of biotin deficiency on *Trypanosoma lewisi* infection in albino rats.** FREDERIC E. CALDWELL and PAUL GYÖRGY. Dept. of Pediatrics and Babies' and Children's Hospital, Western Reserve Univ. In 1943 the authors reported that infections due to *Trypanosoma lewisi* were more prolonged in biotin deficient rats than in normal rats. Further studies have shown that, although the trypanosomes made their appearance in both the normal and the deficient rats at approximately the same time, the appearance of the maximum numbers, initial decline in numbers, and final disappearance of the parasites were all delayed in the biotin deficient rats. Furthermore, about one half of the biotin deficient rats died with large numbers of trypanosomes in their blood as compared to the numbers observed in the normal animals.

The production of ablastin (the reproduction inhibiting antibody of Taliaferro), as evidenced by the continued division of the parasites, was delayed in the biotin deficient rats of the first groups studied. In subsequent experiments serum was obtained from biotin deficient and normal rats at intervals during the course of their infection with *Trypanosoma lewisi*. Passive immunization experiments using these sera also indicated that the ablastin might be strong enough to restrain the trypanosomal reproduction in the biotin deficient animal, nevertheless the ablastic serum from these biotin deficient animals had less protective value than the serum from normal animals. This occurred up to the end of the third week of the infection. Preliminary experiments using the lytic antibodies indicate a similar trend of antibody production.

Rats fed a synthetic diet containing linoleic acid which in previous investigations proved to be toxic (György, P. Tomarelli, R. Ostergard, R. P. and Brown, J. B. J. Experim. Med. 76, 43, 1942) showed infections with *Trypanosoma lewisi* which were neither longer in duration nor higher in numbers than in normal rats.

**The complement fixation test in lymphogranuloma.**

**loma venereum.** MARION E. HOWARD, OLIVE RAY BENHAM (by invitation) and EARLE K. BORMAN (by invitation). *Dept. of Internal Medicine, Yale Univ. School of Medicine, New Haven, Conn. and State Dept. of Health, Hartford, Conn.* Complement fixation tests<sup>1</sup> for lymphogranuloma venereum were performed on 150 sera from persons who were skin tested with human Frei antigen. The results may be tabulated as follows:

No.	Skin reaction intradermal Frei antigen	Lymphogranuloma complement fixation
59	++++	++++
50	0	0
17	++++	0
24	0	++++
150	76	83

There was complete agreement between the results of the intradermal and complement fixation tests in 109 of the 150 sera tested or in 70.3 per cent. 59 of those with positive skin reactions gave positive complement fixation tests though there was no correlation among the size of the skin reactions, the clinical findings and the complement fixing titer. 50 giving no response to the intradermal injection of Frei antigen likewise gave no evidence of complement fixing antibodies in the serum.

Seventeen sera from Frei positive individuals failed to show any evidence of complement fixation for lymphogranuloma venereum. In most instances there was a history suggesting infection with lymphogranuloma venereum in the remote past. The absence of complement fixing antibodies might be interpreted to mean that the infection was burned out as there was no clinical evidence of infection at the time the tests were made; skin sensitivity alone remained. This explanation would be valid were it not for studies in a patient not included in this group with active lymphogranuloma venereum (virus isolated from the lesion) who failed to show complement fixing antibodies in 2 of 3 sera collected over a 3 year period, and only  $\pm\pm$  in a 1:2.5 dilution in a third. Frei tests were always strongly positive in this patient.

There were 24 sera giving positive complement fixation tests from patients whose skin tests were negative. Among these were 7 patients with other venereal diseases in whom infection with lympho-

granuloma might be suspected although no clinical evidence of it was apparent. The remaining 17 gave no history or clinical findings suggestive of venereal infection and the serological tests for syphilis were negative. Among these were 11 cases of cirrhosis of the liver, 1 of infectious hepatitis, 1 with arthritis and pyelonephritis and 4 with primary atypical pneumonia with positive cold agglutinins in 2. The complement fixation test for lymphogranuloma venereum became normal with recovery and the disappearance of demonstrable cold agglutinins in one of these. It would seem from these data that further study is required for a proper evaluation of the complement fixation test as a diagnostic measure of infection with lymphogranuloma venereum.

**Selective inhibitory action of tuberculo-carbohydrate and phosphatide on cellular cathepsins from tuberculous tissues.** CHARLES WEISS<sup>1</sup> and NELLIE HALLIDAY.<sup>2</sup> *Research Labs. of the Mount Zion Hospital, San Francisco, Calif.* Several investigators, including Moen, have suggested that the specific toxic action of tuberculin upon hypersensitive tissues is probably not the result of an antigen-antibody reaction. Our data tend to support this viewpoint. We have observed a selective inhibitory action of tuberculo-carbohydrate and tuberculo-phosphatide upon endocellular enzymes (Cathepsin II) derived from tissues of animals infected with tubercle bacilli. On this basis the following enzymological explanation is proposed: Since cathepsin is the enzyme which is concerned with the processes of cellular growth and repair, inhibition thereof leads to injury of the cells. Tuberculin is more toxic for tuberculous than for normal cells in tissue culture because two of its important constituents (phosphatide and carbohydrate) exert a selective inhibitory action upon the proteinases of the former.

Our observations may also throw light on the mechanism of cäsation and softening. As pointed out by Jobling and Petersen, "Cäsation in tuberculosis is a form of coagulation necrosis in which the dead tissues rarely undergo autolysis, except as a result of secondary infection". It is quite likely, therefore, that inhibition of autolysis is accomplished by the carbohydrate and phosphatide fractions of the tubercle bacilli.

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<sup>1</sup> The antigen used was lygratum CF supplied by Squibb & Sons.

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The following abstract was inadvertently omitted from those of the American Physiological Society in the March issue.—Ed.

**On the mechanism of platelet agglutination.** ALFRED L. COBLEY (introduced by W. H. Howell) and RALPH B. HOULIHAN. *Depts. of Surgery and Bacteriology, Univ. of Virginia School of Medicine, Charlottesville.* We developed a macroscopic platelet agglutination method to test the agglutinability of various platelet suspensions and substances effecting platelet agglutination. The development of this agglutination method was made possible with our method of isolating platelets from whole blood made incoagulable by the addition of sodium citrate, magnesium sulfate, sodium oxalate, heparin, or by dilutions of blood with 10 to 15 volumes of physiologic saline (Copley and Houlihan, *Science*, 1944, 100: 505). These platelet suspensions, thoroughly washed free of red cells, white cells and plasma, were dispersed and stable in saline.

<sup>1</sup> The products of plasma fractionation employed in this work were developed from blood, collected by the American Red Cross, by the Department of Physical Chemistry, Harvard Medical School, Boston, Massachusetts, under contract recommended by the Committee on Medical Research, between the Office of Scientific Research and Development and Harvard University.

The agglutination method was standardized since time and temperature of incubation and the concentration of platelets in suspension affected the intensity of agglutination.

Platelets obtained from different blood-anticoagulant systems of humans and dogs varied in their agglutinability as did platelets from different humans or animals. A platelet suspension from one subject showed significant variations in the degree of agglutinability when tested with plasmas and sera from different subjects. Agglutination of platelets was obtained with purified globulin fractions (Harvard<sup>1</sup>), purified prothrombin and thrombin (Seegers and Harvard<sup>1</sup>), placental tissue juice, and, interestingly, plasma containing heparin in high concentrations. Crystalline and crude albumins (Harvard<sup>1</sup>) agglutinated platelets either slightly or not at all. However, purified fibrinogen (Harvard<sup>1</sup>), and placental and plasmatic thrombo-plastic substances prepared according to Copley (*Science*, 1945, 101: 436) never caused agglutination. Our studies indicate that the agglutination of platelets is not brought about by fibrin formation and that the two processes are governed by different mechanisms.

## CORRECTION OF ERRORS IN LAST (MARCH, 1945) ISSUE

Page 4. T. C. Barnes and R. Beutner. This abstract was repeated by mistake on page 5 (*The healing index of human skin determined by an electrical method*, T. C. Barnes). The latter was submitted as a revised version of the first abstract.

Page 5. T. C. Barnes and R. Beutner. At the end of the first paragraph at the top of the second column add the phrase: "on addition of 0.05% acetylcholine."

Page 10. Paul C. Bucy. Correct title to read: "Abolition of tremor by removal of area 4γ."

Page 43. E. M. Landis, E. D. Thomas and J. E. Wood. Last paragraph, top of p. 44, lines 2 and 5, correct word "hypertension" to read "hypotension."

Page 50. J. F. McClendon. Tenth line of second paragraph. Correct sentence beginning "If a normal . . ." to read: "If a normal segment and an inside-out segment are cut longitudinally the motor activities of the two are the same." The following sentence should then read: "If a cut segment is sewed up its activity returns to the level before cutting."

Page 51. A. T. Miller, Jr. The sentence beginning: "(5) Plasma volumes at these sampling times . . ." (line 12, p. 52) should read: "(5) Plasma

volumes at these sampling times ( $PV_n$ ) are calculated from the formula  $PV_n = D_s/D_n \times PV_n$ , where  $D_n$  = dye concentration of the sample,  $D_s$  = dye concentration on the reference disappearance curve at the corresponding time and  $PV_n$  = reduced plasma volume . . ."

Page 104. Albert E. Sobel and Harold Werbin.

(1) In paragraph 2 line 3  $E_{1\text{cm.}}^{1\%}$  of 1710 should read  $L_{1\text{cm.}}^{1\%}$  of 1385.

(2) In paragraph 2 line 6  $E_{1\text{cm.}}^{1\%}$  of 1240 should read  $L_{1\text{cm.}}^{1\%}$  of 1010.

Page 105. M. Spiegel-Adolf and E. Spiegel. In the first sentence the "and" after the word "convulsions" should be "end" so that the last clause of the sentence reads: "before the convulsions end absorption only."

Page 161. W. A. Perlzweig, J. M. Ruffin and D. Cayer. The sub-heading of the table, "Lowest normal decile," should be moved to the extreme right so as to cover the last three columns only, the table heading thus arranged:

### 2 HOURS' EXCRETION TEST

Subjects	No.	Range	Mean	S.D.	Lowest normal decile		
					Range	No.	%

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*Representatives on the Council of the American Association for the Advancement of Science:* P. A. Shaffer, V. du Vigneaud.

*Representative on the Control Committee of the Federation Proceedings:* C. G. King.

ARNOLD KENT BALLS  
*Secretary*

### THE AMERICAN SOCIETY FOR PHARMACOLOGY AND EXPERIMENTAL THERAPEUTICS, INC.

#### ABSTRACT OF COUNCIL PROCEEDINGS

1944-45

*May 1944:* The results of the by-mail election were as follows:

1. *Officers:* President, Erwin E. Nelson; Vice-President, Charles M. Gruber; Treasurer, McKeen Cattell; Secretary, Raymond N. Bieter; Councilors, Harry Beekman and Nathan B. Eddy; Editor, George B. Wallace; Membership Committee, Carl A. Dragstedt and Carl F. Schmidt; Nominating Committee, Herbert O. Calvery, Arthur C. De Graff, James M. Dille, Benjamin H. Robbins, Frederick F. Yonkman.

2. *New Members:* O. W. Barlow, Allan D. Bass, T. J. Becker, Karl H. Beyer, C. I. Bliss, H. F. Chase, Graham Chen, S. C. Cullen, E. J. de Beer, R. H. K. Foster, Nicholas Fugo, W. M. Govier, E. Ross Hart, L. W. Hazelton, S. Krop, W. S. Lawrence, E. L. McCawley, R. Mendez, Walter Modell, Gordon K. Moe, James Morrison, Ernst Oppenheimer, O. S. Orth, E. Rovestine, F. E. Shideman, R. B. Smith, G. W. Stavraky, M. R. Thompson, Clara Torda, Klaus Unna, J. A. Wells, A. Wikler, Edwin G. Williams.

During the ensuing nine months plans were made to hold the Annual Meeting in Cleveland, Ohio, May 6-8, 1945. These plans were abruptly terminated by the ruling of the Office of Defense Transportation which denied the application of The Federation to hold this meeting.

*September 1944:* The Treasurer, Dr. McKeen

Cattell, was instructed to send Dr. Hooker, Federation Secretary-Treasurer a check for \$307.00 (\$1. per member) for the Federation Proceedings.

*February 1945:* In lieu of an Annual Meeting abstracts were collected and published in the Federation Proceedings.

*May 1945:* The Council voted to hold a Council Meeting in Cleveland, Ohio on June 10, 1945 to conduct the necessary affairs of the Society. A notice was sent to the members on May 19, 1945 informing them of this meeting. This notice also included the names of 31 Proposals for Membership.

#### ABSTRACT OF COUNCIL MEETING

JUNE 10, 1945

The meeting was called to order by the President in the Library of the Department of Pharmacology of the Western Reserve University School of Medicine at 10 A.M. Those present were: E. E. Nelson, President; Charles M. Gruber, Vice-President; McKeen Cattell, Treasurer; Harry Beekman, Councilor; Nathan B. Eddy, Councilor; H. B. Haag, Chairman, Membership Committee; Raymond N. Bieter, Secretary.

The reading of the minutes was dispensed with since they were approved by last year's Council.

The Secretary read the abstracts of the Council Proceedings for 1944-45. These were approved for publication in the Federation Proceedings together with this abstract of the Council Meeting.

*Reports received, read and accepted.* In each instance it was voted to instruct the Secretary to file the complete report.

1. Report of Dr. Torald Sollmann, Society Representative, on the meeting of the Union of American Biological Societies in December 1944 in Cleveland.

2. Report of The Journal Editor, Dr. George B. Wallace.

3. Report of the Treasurer, Dr. McKeen Cattell. The President appointed Drs. H. B. Haag and Arnold Welch auditors. The auditors approved the report.

4. Report of the Membership Committee, submitted by the Chairman, Dr. H. B. Haag. As a result of the joint meeting with the Council, a list of 18 names will be submitted to the members of the Society. The ballot, to be submitted by mail, was approved by the Council.

Dr. Gruber moved that the dues for the coming year be \$3. This was approved.

Dr. Eddy moved that the President appoint a long range planning committee to consider the financial plans of the Society, to be reported to the next Council Meeting for recommendation to the next annual Society Meeting. This was approved.

From time to time it has been the policy of the Society to make contributions to the Union of American Biological Societies. It was approved that the Society send \$20. to the Union of American Biological Societies.

Concerning the question of a by-mail election of officers, the following motion was passed unanimously: "It was moved that the question of election of officers be submitted to the members and that the members be notified that the Nominating Committee has submitted a slate of nominations in a sealed envelope. If a majority of the votes cast favor an election of officers this sealed envelope shall be opened and the report inside shall be taken as the slate of nominations. A member may submit a slate of nominations. If a majority of the voting members submit the same name for an office, that name shall be added to the slate of the Nominating Committee."

A list of names for a new Nominating Committee was selected by the Council. This list will be submitted to the members for a by-mail election.

*Deceased member:* Barkan, George, March 7, 1945.

RAYMOND N. BIETER  
*Secretary*

## AMERICAN INSTITUTE OF NUTRITION

### RÉSUMÉ OF COUNCIL MEETING,

APRIL 6, 1945

The regular meeting of the Federation having been cancelled, the Council of the American Institute of Nutrition met in Detroit on April 6, 1945. Drs. Macy-Hoobler, Rose, Jukes, Elvehjem, and Smith were present.

After discussion of the work of the Control Committee of FEDERATION PROCEEDINGS, Dr. Smith was requested to continue as representative of the Institute on the Control Committee for the coming year. The managing editor was commended for efficient handling of the affairs of FEDERATION PROCEEDINGS to date.

The request for participation in the program of the Union of American Biological Societies was tabled until it could be discussed in open meeting.

The following names were approved for election to membership: Robert V. Boucher, W. M. Cox, Jr., Leopold R. Cerecedo, William J. Darby, Philip L. Harris, Millicent L. Hathaway, Charles L. Hoagland, John C. Keresztesy, Herbert E. Longnecker, Margaret A. Ohlson, Bernard L. Oser, L. Bradley Pett, John Vincent Seudi, Sedgwick E. Smith, Roger J. Williams.

The Treasurer's report, audited by Drs. Tolle

and Kline, was presented. As of March 1, 1945, there is a balance of \$773.83.

The Report of the Editor of the JOURNAL OF NUTRITION was presented. During 1944 there was a drop in the number of papers submitted from 176 in 1943 to 155 in 1944. Of the latter number 103 were accepted and published. By skillful adjustment to the necessity of saving paper, surprisingly little change resulted in the number of papers published. Labor difficulties interfered with prompt publication at times. The Editor paid tribute to the efficient cooperation of the Director of the Wistar Institute in the manifold problems of publication of the JOURNAL.

The proposed changes in the By-Laws were reviewed and approved by the Council.

The Secretary reported that Dr. D. W. Woolley had been selected by the Committee of Judges to receive the Mead, Johnson and Company Prize and that the Borden Award in Nutrition had been given to Dr. H. H. Mitchell.

The dues for 1945-46 were fixed at \$2.00 and it was agreed that \$1.00 per member be paid from the treasury in support of FEDERATION PROCEEDINGS. As before \$25.00 each was designated for the Secretary and Treasurer for secretarial assistance.

The Secretary called attention to the symposium

sponsored by Dr. C. G. King for publication in  
FEDERATION PROCEEDINGS.

President Macy-Hoobler appointed the follow-  
ing Nominating Committee for the coming year:

Dr. A. G. Hogan, Chairman, Drs. H. Goss, A. D.  
Holmes, I. McQuarrie and Lydia J. Roberts.

ARTHUR H. SMITH  
Secretary

## PAPER PREPARED FOR PRESENTATION BEFORE THE JOINT SESSION OF THE FEDERATION, 1945

### THE ANTICOAGULANT 3,3'-METHYLENEBIS(4-HYDROXYCOUMARIN)<sup>1</sup>

KARL PAUL LINK

*Wisconsin Agricultural Experiment Station, University of Wisconsin, Madison*

3,3'-Methylenebis(4 - hydroxycoumarin) is the causative agent of the hemorrhagic disease of cattle known in agricultural practice as "sweet clover disease" (1). This disease arises from the eating of improperly cured hay or silage made from the common sweet clovers *Melilotus alba* and *M. officinalis*. Its occurrence was originally observed practically simultaneously in Canada by Schofield (2) and in this country by Roderick (3).

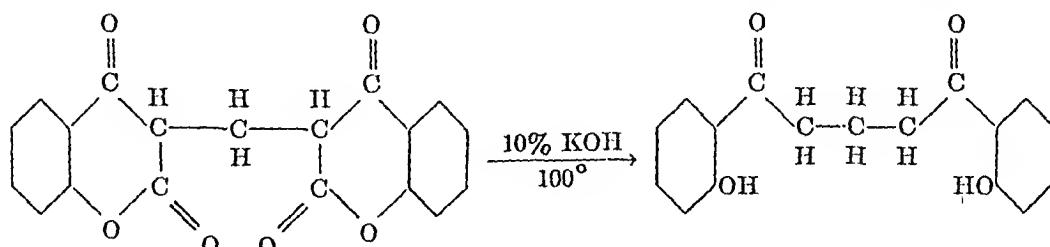
The characteristic lesion of the disease is hemorrhage resulting from loss of clotting power of the blood, apparently due primarily to a prothrombin deficiency (Roderick 3). It was recognized by Schofield and Roderick that the disease could be controlled by the withdrawal of the spoiled hay from the diet and by transfusion of blood freshly drawn from normal cattle, provided the hemorrhagic extravasation had not proceeded too far. No visible alteration was found in the blood vessels to explain the internal hemorrhagic diathesis, but external hemorrhage may be readily induced by surgical treatment (castration or dehorning) or accidental injuries.

The pure anticoagulant  $C_{19}H_{12}O_6$ , m.p. 288-289° was isolated by H. A. Campbell from spoiled sweet clover hay that had killed cattle in agricultural practice and from hays artificially spoiled (4). In the isolation studies the Quick one-stage method for estimating prothrombin was employed to follow the course of the fractionation after it was demonstrated that the use of appropriately diluted plasma (plasma concentration range 25 to 5 per cent) permitted the detection of smaller changes in the prothrombin level (or activity). This saved the lives of many valuable individually standardized assay rabbits and also made it possible to follow the progress of the isolation scheme with a high degree of certainty (5).

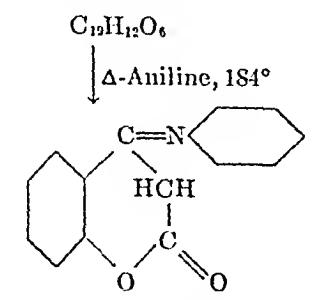
The chemical identity of the anticoagulant was revealed by Stahmann and Huebner (6, 7) through degradation reactions and by synthesis according to the formula indicated.

<sup>1</sup> Paper Presented before the Joint Session of the Federation.

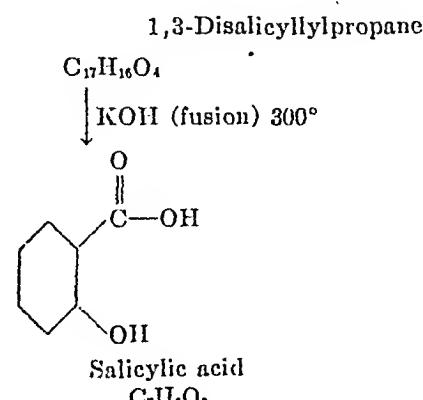
#### Degradation of 3,3'-methylenebis(4-hydroxycoumarin) under alkaline conditions

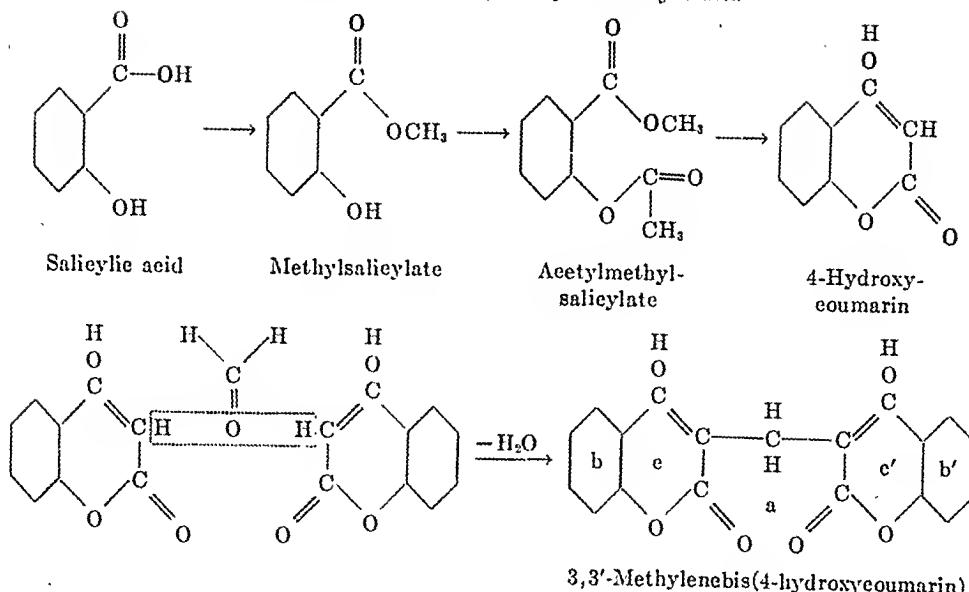


Keto form of 3,3'-methylenebis (4-hydroxycoumarin)



Anil of 2,4-Diketochroman  
 $C_{19}H_{11}O_2N$



*Synthesis of the anticoagulant from salicylic acid**Chemical properties of the anticoagulant (6, 7).*

It is apparent that tautomeric modification of 3,3'-methylenebis(4-hydroxycoumarin) into 3,3'-methylenebis(2,4-diketochroman) is possible. To this reversible transformation is ascribed, *inter alia*, the acidic properties of the substance, its behavior toward carbonyl reagents, and its degradation by alkali. Thus salt formation, methylation and acetylation of the enol form of the substance would be expected (4). The cleavage caused by the base aniline may be considered a reverse aldol condensation (6). The mild alkali treatments affect opening of the lactone rings to produce a  $\beta$ -keto acid which would dearboxylate readily to the  $\delta$ -diketone. Stronger alkali effects cleavage of the double bond to the enol form of the diketone to produce salicylic acid (7). The insolubility of 3,3'-methylenebis(4-hydroxycoumarin) in water, its low solubility in the common organic solvents and solubility in alkaline media (salt formation) are worthy of special note (4). To date this is the only biscoumarin derivative found in nature (8).

*Structure and hypoprothrombinemic action in the 4-hydroxycoumarin group.* In view of the structure of 3,3'-methylenebis(4-hydroxycoumarin) analogues were prepared wherein substitution was effected on (1) the methylene carbon atom, a; (2) the benzene rings b, b'; and (3) acyl and alkyl substitution of the hydroxyl group on the  $\alpha$ -pyrone rings, e, e'. In addition various 3-substituted-4-hydroxycoumarins, as well as degradation products of the methylenebisoumarin and 4-hydroxycoumarins were studied. Of some 150 compounds in this group, the parent substance proved to be the most potent, based on the maxi-

mum response per millimole of test substance evoked by a single oral dose, with standardized rabbits as the test animal. The biological activity phase of this study has been summarized in (9) and the chemical aspects in (10-15). The overall findings have been confirmed by others (16, a, b, c).

*The effect of the anticoagulant on the plasma.* It should be noted that 3,3' - methylenebis(4-hydroxycoumarin) after action *in vivo*, impairs or prevents the coagulation of blood. The syndrome produced by feeding it to experimental animals if not allowed to proceed too far (or long) apparently does not result in permanent injury. Extensive control studies indicated that animals do not acquire immunity or increased susceptibility to the anticoagulant (5). It is therefore possible to use the same animal repeatedly after allowing a brief period for recovery. Some rabbits and dogs have been used in our laboratory for over 200 individual assays extending over a period of 4-6 years (17).

The prothrombin time of 12.5 per cent plasma will indicate the onset of the hypoprothrombinemia before changes in the prothrombin time of the whole plasma can be detected, the whole blood clotting times will usually be unaffected when the reduction in the prothrombin level (or activity) becomes detectable; and finally in normal animals hemorrhage does not occur unless 3,3'-methylenebis(4-hydroxycoumarin) is fed or injected continuously over a period of time (17).

Figure 1 shows the response evoked in carefully standardized rabbits. Other species (mouse, rat, guinea pig, dog and man) respond essentially like the rabbit. The important points are (a) the lag in

the response, (b) the variation in the intensity and (c) the variation in the duration of the hypo-prothrombinemia with the dose. In 2.5-3.0 kilo rabbits under our conditions the most efficient response is evoked by 0.75 mgm. Below this level the efficiency of action is decreased by a threshold effect and at high levels by incomplete absorption. The same holds in principle with all species studied to date.

According to Quick (18, 19) prothrombin is composed of two components (A and B) which are linked through calcium and it is the B component that is decreased by this anticoagulant. We have not been able to confirm this (unpublished). The work and views of Seegers et al (19a) sustain our findings. The mechanism through which 3,3'-methylenebis(4-hydroxycoumarin) reduces the prothrombin level (or activity) is still obscure—but the bulk of the evidence suggests that the syn-

that high doses (10-15 mgm./kgm.) usually tend to decrease the fibrinogen level. However, when the anticoagulant is fed at the levels which give a readily detectable and safely maintainable increase in the prothrombin time (2 to 4 mgm./kgm. or less) the fibrinogen values usually fall within the range obtained with normal animals. In sum when the anticoagulant is fed at low levels, we have so far not been able to draw any correlations between reduction in prothrombin level (or activity) and fibrinogen response. In this connection the over-all conclusions of Foster and Whipple (21) should be borne in mind, to wit that fibrinogen is an extremely labile plasma protein constituent, and fluctuations in content can be brought on by a number of factors.

*Toxicity of the anticoagulant.* As the hemorrhagic sweet clover disease occurs in agricultural practice Roderick could find no visible alterations in the blood vessels to explain the internal hemorrhagic diathesis (3). Meyer and coworkers noted that the repeated administration of the anticoagulant to dogs in toxic doses, causes a profound vaso-dilatation of capillaries, small arteries and veins (22). This was confirmed by Dale and Jaques (23) and Bollman and Preston (24). Chen and co-workers (25) determined the toxicity in rabbits, rats, mice, guinea pigs and dogs and established the median lethal doses. Most animals dying from the action of the anticoagulant develop hemorrhage into various organs and tissues and pulmonary edema. Central necrosis of the liver was observed in about one-half of the rats examined and occasionally in rabbits, mice and dogs. Richards and Cortell (26) made post-mortem studies on a group of dogs, monkeys and guinea pigs that had received toxic doses of the anticoagulant and found necrosis of the liver. Roderick reported that cattle dying of the hemorrhagic sweet clover disease in agricultural practice showed no evidence of pathologic change in the liver (3). The work of Meyer (22), Bollmann (24), Lehmann (27) and Dam (28) indicates that the anticoagulant produces little, if any morphological damage to the liver and that when such damage is found it is usually secondary to local hemorrhage. Liver function tests likewise show no detectable impairment of the organ (22, 24, 27).

*Vitamin K and the anticoagulant.* At very low levels (those regarded as effective for a nutritional deficiency of vitamin K) 2-methyl-1,4-naphthoquinone does not prevent the hypoprothrombinemic action of the anticoagulant (5). But Overman and Stahmann (29) showed that the oral administration of the quinone to rabbits at high levels reduced the extent and duration of the action of a single dose of the anticoagulant (see fig. 2). Next, Overman, Field and Baumann (30) showed that in the rat all the biologically active forms of

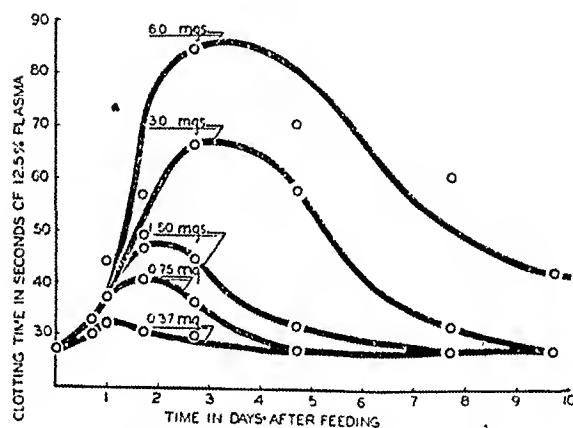


Fig. 1. The effect of feeding different levels of 3,3'-methylenebis(4-hydroxycoumarin) on the 12.5 per cent plasma prothrombin time of a group of standardized rabbits (average curves for six animals).

thesis is prevented. This might be either through some mechanism that prevents vitamin K from catalyzing pro-thrombin synthesis or to a direct action on the prothrombin.

Roderick concluded that as the hemorrhagic sweet clover disease occurs in agricultural practice there may be some depression in fibrinogen levels, yet the values obtained were within the range of values observed with normal animals (3). Unpublished data obtained here over a period of years sustains this statement. Recently Irish and Jaques (20) reported in a very carefully executed study that when the anticoagulant is injected intravenously into dogs at high levels (15-20 mgm./kgm.) a detectable decrease in plasma fibrinogen results, while smaller doses (5 mgm./kgm.) tend to increase the fibrinogen level. We have concentrated on the response of various species to the oral administration of the anticoagulant and have noted

vitamin K are not only very effective in counteracting the action of a single dose of the anticoagulant, but also prolong the lives of rats fed doses that would be highly toxic on diets free from vitamin K. Contrary to the numerous initial clinical reports, it is now also perfectly clear that vitamin K can counteract the hypoprothrombinemic action of the anticoagulant in man. Shapiro (31) and Lehmann (27) were the first to demonstrate this effect in man, and were subsequently confirmed by others (32, 33, 34). In an excellent study, Cromer and Barker (35) reported that the administration of menadione bisulfite intravenously in doses of 64 mg. to patients who exhibit excessive prothrombin deficiency after administration of

showed that rats fed a diet of condensed milk can be protected against the hypoprothrombinemia by the administration of any one of a number of substances like carvone and chloretone, that increase the synthesis of vitamin C. Indeed, carvone and chloretone can prolong the survival time of rats fed the anticoagulant (36). With the guinea pig, Sullivan et al. (37) showed that massive doses of 1-ascorbic acid counteract the action of the anticoagulant, in that they prolong the survival times of animals receiving daily small doses of the anticoagulant. When a single dose of the anticoagulant is given to scorbutic guinea pigs, the extent and duration of the hypoprothrombinemia are both drastically prolonged (37). The similarities in the gross pathological effects of deficiencies of vitamin C and K and of the continuous administration of the anticoagulant suggests that

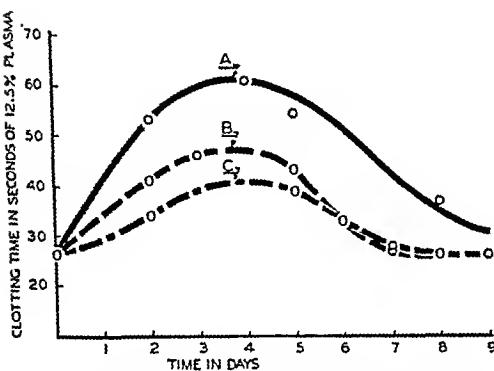


Fig. 2. The effect of 2-methyl-1,4-naphthoquinone on the action of 3,3'-methylenebis(4-hydroxycoumarin) in rabbits. Curve A is the response of ten rabbits fed 3 mgm. of the anticoagulant alone; curve B when 30 mgm. of vitamin K were fed with 3 mgm. of the anticoagulant; curve C when 30 mg. of vitamin K were fed 3 days prior to and each day after feeding 3 mgm. of the anticoagulant.

the usual doses of "Dicumarol,"<sup>2</sup> definitely increases the safety factor of "Dicumarol" therapy.

*Vitamin C and the anticoagulant.* The oral administration of 1-ascorbic acid at high levels alone with moderate single doses of the anticoagulant prevented the usual increase in the prothrombin time in some rabbits (29). The simultaneous oral administration of 1-ascorbic acid and 2-methyl-1,4-naphthoquinone at high levels to rabbits along with a single dose of the anticoagulant either drastically reduced or completely nullified the hypoprothrombinemic action (29). While 1-ascorbic acid does not counteract the anticoagulant in the rat, Baumann et al. (36)

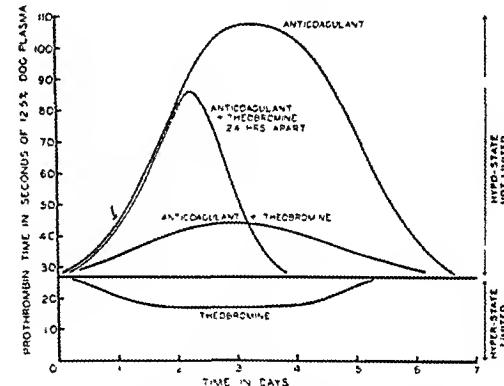


Fig. 3. Representative chart of the protective action of theobromine against 3,3'-methylenebis(4-hydroxycoumarin) in the dog. Theobromine, 100 mgm. per kilo and 3,3'-methylenebis(4-hydroxycoumarin) 10 mgm. per kilo, given orally.

the action of 3,3'-methylenebis(4-hydroxycoumarin) may in part be due to disturbances in the metabolism of vitamin C and the antihemorrhagic quinones in the animal body (29, p. 161).

*The effect of methylated xanthines on the action of the anticoagulant.* One of the interesting and unpredictable observations that has arisen from our work on the anticoagulant has dealt with the hypercoagulable effects induced by caffeine, theophylline and theobromine. Field, et al. (38) found that single oral doses of these methylxanthines induce in the dog, rabbit and rat, a state of hyperprothrombinemia and that they also increase the fibrinogen level (39). The resulting hypercoagulability from a single oral dose persists in the dog for 4 to 5 days and repeated small doses can maintain the hyperprothrombinemic state and the increased fibrinogen levels for periods up to 30

<sup>2</sup> Dicumarol is the trademark for the synthetic preparation 3,3'-methylenebis(4-hydroxycoumarin).

days. The methylxanthines can also counteract the hypoprothrombinemic action of 3,3'-methylenebis(4-hydroxycoumarin) in the dog. When they are given either with, or 24 hours after the anticoagulant, they not only reduce the intensity of the hypoprothrombinemic response but also shorten its duration. It was suggested that the methylxanthines produce a functional stimulation of hepatic tissue, which accounts for the increased prothrombin and fibrinogen levels in normal animals and for the protective action against the anticoagulant. The possible bearing of these findings on the use of methylxanthines in conjunction with cardiovascular therapy was raised in the original publication (38).

*Hypoprothrombinemia induced by salicylic acid.* The quantitative *in vitro* chemical degradation of 3,3'-methylenebis(4-hydroxycoumarin) to sali-

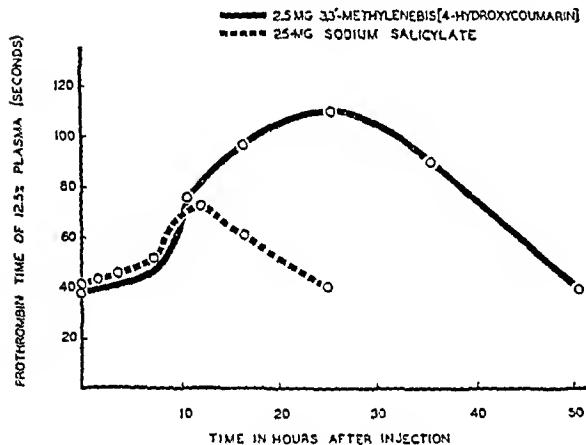


Fig. 4. The comparative effect of sodium salicylate and 3,3'-methylenebis(4-hydroxycoumarin) given intravenously on the prothrombin time of 12.5 per cent plasma (average response of six rats).

cyclic acid was achieved by Huebner in the characterization and identification studies (6, 7). Although a comparable degradation *in vivo* has as yet not been established (1) it was found that salicylic acid can induce hypoprothrombinemia and hemorrhage in rats fed a diet low in vitamin K (40). When the rats were fed a natural grain ration, or one containing 2-methyl-1,4-naphthoquinone, salicylic acid failed to induce hypoprothrombinemia. In other words, vitamin K counteracts this particular effect of the salicylates. Salicylic acid proved to be about  $\frac{1}{10}$  as active as the bis-coumarin (fig. 4) and it appears that in the rat acetylsalicylic acid (aspirin) is more potent than salicylic acid or sodium salicylate (1, p. 199). Subsequently as a result of our studies, the hypoprothrombinemia inducing capacity of the commonly used salicylates was demonstrated on man by Shapiro et al. (41); Meyer and Howard (42),

Rapoport et al. (43), Fashena and Walker (44) even when the diet is not restricted. Furthermore, the clinicians Shapiro and Meyer have shown that vitamin K counteracts the hypoprothrombinemic effect of salicylates in man, just as it does in the rat (41, 42).

Hemorrhagic complications in conjunction with salicylate intoxication have recently again been reported<sup>3</sup> (45, 46). In the original publication (40) we did not write nor imply that when hemorrhage does arise from salicylate medication that it was due solely to the induced hypoprothrombinemia. In contrast it was stated that the findings with the rat offered "at least a partial explanation for one of the untoward effects that they (the salicylates) might induce under certain conditions". It appears from some of our unpublished work that the action of the salicylates on the blood coagulation components is not restricted to the prothrombin activity, but that the fibrinogen level can also be effected. Furthermore, since general vascular damage invariably results from salicylate intoxication it is conceivable that hemorrhage may take place without complete depletion of the essential plasma protein clotting components. Fashena and Walker (44) have recently published a thorough review of the broad problem of salicylate intoxication and this has been followed by an objective editorial in J. A. M. A., p. 460, February 24, 1945. Now that clinicians are aware of the effect of salicylates on the clotting mechanism it will be interesting to see to what extent the use of vitamin K will reduce the hazards of hemorrhagic complications after salicylate administration, especially in the treatment of rheumatic fever for which, according to Hanzlik they are the "sovereign remedy" (47, p. 4).

*Other physiological factors that influence the action of the anticoagulant.* Field et al. (48) made the interesting observation that pregnant and lactating rats tolerate higher levels of the anticoagulant than normal females. In an extension of this study Field showed (49) that the continuous feeding of the anticoagulant to female rats with suckling pups caused the pups to become hypoprothrombinemic and subject to hemorrhage. Acetylsalicylic acid caused the same response. Vitamin K showed a protective effect more apparent in the pup than in the mother. It is not known at present whether the anticoagulant fed to the suckling female rat passes directly into the milk or whether an active metabolite from it is the cause of the hypoprothrombinemia and hemorrhage in the suckling young. Although it would appear that the mammary gland is per-

<sup>3</sup> See reference (40) and the Harvey Lecture (1) for the earlier literature on hemorrhage rising from salicylates.

meable to vitamin K, it cannot now be stated that the protective action of the quinone is due to the transmission of the intact molecule or to an active metabolite. The observations on pregnant and lactating rats hold also for the dog (unpublished work of Field, Spero and Link) Davis and Porter (50) have recently reported favorable clinical results in the treatment of puerperal thrombosis with 3,3'-methylenebis-(4-hydroxycoumarin). It would appear that when this anticoagulant is used in this disorder, the suckling infant should either be withdrawn from the mother when the drug is given or the prophylactic administration of vitamin K to the infant be considered (49).

*3,3'-Methylenebis(4-hydroxycoumarin) in the prevention of thrombosis.* One of the significant points that has been established since the anticoagulant has become available is that a primary relationship exists between thrombus formation and the clotting mechanism of the blood. This was first established by Dale and Jaques (23) and independently confirmed by others (24, 26, 51). These studies on experimental thrombosis established for the first time that an effective reduction of extravascular and intravascular thrombus formation parallels a diminished plasma prothrombin level (or activity) with its associated hypocoagulability.

Baronofsky and Quick showed that the anticoagulant decreased platelet agglutinability (52) and Spooner and Meyer (53) reported that a definite decrease in platelet adhesiveness accompanies the hypoprothrombinemia in man. Since the inhibition of platelet agglutination is a primary factor in the prevention of thrombosis it appears that the clinical use of 3,3'-methylenebis(4-hydroxycoumarin) as a prophylactic agent of thrombosis rests on a sound basis (54).

*Indications and clinical use of 3,3'-methylenebis(4-hydroxycoumarin) [Dicumarol].* "Dicumarol" is recommended for the prophylaxis and treatment of intravascular clotting (54-62). It is being used alone or as an adjunct to heparin in the treatment of postoperative thrombophlebitis and pulmonary embolism, acute embolic and thrombotic occlusion of peripheral arteries, recurrent idiopathic thrombophlebitis, post-traumatic and postinfectious thrombophlebitis and pul-

monary embolism. The drug does not exert a resolving effect on thrombi or emboli already present and there is no indication at present that it will increase the blood supply of an area infarcted by an embolus. The use of the drug in these cases can only be expected to retard intravascular clotting and prevent propagation of the thrombus or embolus. Since the ultimate outcome of acute coronary thrombosis is to a large extent dependent on the extension of the clot and on the formation of mural thrombi in the heart chambers with subsequent embolization the drug has been used as an adjunct in treating this condition. The transfusion of freshly drawn citrated blood and the intravenous administration of a water soluble form of vitamin K in a dosage comparable to 40 mg. of menadione readily counteracts an excessive "Dicumarol" effect (35, 62).

The clinical use of "Dicumarol" must be controlled by daily prothrombin determinations, for altering the coagulability of the blood, that protective mechanism of life *par excellence*, is in principle a hazardous business (1). Little difficulty has been experienced by some clinicians in the prophylactic use of the anticoagulant. See for instance (35, 56, 57, 58, 59, 60, 61, 62). The hasty and the ill-prepared have run into the obvious difficulties. It would appear that faulty technique in the estimation of prothrombin activity is quite common. A capital factor in the success of our work with experimental animals has been the use of 12.5 per cent, as well as whole plasma (5). Its use involves merely making a dilution of 1 part whole plasma with 7 parts physiological saline solution. Through the use of diluted plasma the lives of many valuable assay rabbits were saved in the arduous road that Campbell had to travel to isolate the anticoagulant from the spoiled sweet clover hay (1). With 12.5 per cent plasma the protective action of vitamin K against the anticoagulant was first detected, the hypoprothrombinemic action of the commonly used salicylates discovered and the hyperprothrombinemic action of the methylxanthines demonstrated. Is there any reason why human subjects should not be given the benefit of a prothrombin technique (63) (64) that has made it possible to make these discoveries with experimental animals?

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*American Physiological Society***SYMPOSIUM ON CARDIAC OUTPUT**

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The problem of measurement of cardiac output in man has in the last few years received renewed attention as a result of the development of two methods, the ballistocardiograph and the Direct Fick, based on entirely different principles.

The principle involved in the first method is, that forces originating in the movement of blood are transmitted to the body and can therefore be recorded. A student of this method is faced first with the problem of recording these forces unaltered. He is confronted then with a choice among the physical entities related to movement of blood, i.e., variations in mass and acceleration, secondary vibrations, instantaneous flow intensity etc., and with the most difficult problem of working out a general formula relating the recorded forces and the chosen physical entities: a problem of Analytical Dynamics requiring a profound knowledge of this branch of higher mathematics. The last difficulty is to finally derive a practical formula for the calculation of cardiac output; a formula which may be applicable to all possible variations of the stroke volume in health and disease. Once these difficulties are overcome, measurement of cardiac output would require simply that the subject under investigation should stand or lie on the recording apparatus with a technician supervising the details of recording.

The second method, in contrast to the first, is based on a simple principle, enunciated by Fick, which could not be applied to man until recently

because of technical difficulties in obtaining samples of mixed venous blood for analysis, without danger or discomfort to the subject. With this method the problem to solve was the development of a safe technique and the demonstration of the validity of the samples collected.

Among the investigators of the first method there is still controversy as to the required mechanical characteristics of the recording apparatus, the physical entities involved and the mathematical approach to an empirical or rational formula. Differences among the proponents of the second method are of a less serious nature, dealing chiefly with minor considerations concerning technique, with definition of physiological states or with interpretation of findings in a field of study of the circulation in man, constantly expanding. As this symposium progresses, it will become apparent that the controversy is not limited strictly to each camp separately.

An historical background is provided for by W. F. Hamilton, whose critical analysis of most of the methods of measurement of cardiac output used up to this date in man, is certainly one of the most stimulating contributions to this Symposium. It seemed appropriate to publish, as a separate article, notes sent to me personally by John McMicheal from London, who worked with the Direct Fick method under most adverse circumstances.

**NOTES ON THE DEVELOPMENT OF THE PHYSIOLOGY OF CARDIAC OUTPUT**

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During the first quarter of the present century the serious attempt to study the cardiac output of man was begun. There developed two antagonistic schools of thought as to the quantities involved. These schools had their headquarters in Copenhagen on the one hand, and in Oxford on the other. By means of the nitrous oxide method, Krogh and Lindhard (1) settled on the theory that the cardiac output of resting man is 3.5-4.5 l. per min. Krogh, Lindhard, Liljestrand, and

their co-workers published a long series of papers (see 2) using the nitrous oxide method and supporting the idea that the output of the human heart was of this order. In addition, Bornstein's nitrogen method gave results of the same size (3).

At about the same time, Christiansen, Douglas, and Haldane (4) studied the cardiac output by means of pulmonary CO<sub>2</sub> tensions and came to the conclusion that the heart pumped five to eight liters instead of the 3 to 5 of the Scandinavians

(5). This idea was widely promulgated in the United States. Henderson (6, 7, 8, 9) led in the effort and many followed (10, 11, 12, 13 among others) all of whom demonstrated to their own satisfaction that the heart pumps out 5-8 liters. Of course there were some workers who included in their series men whose hearts were said to pump large quantities of blood and men whose resting output was small. They did not commit themselves either way (14, 15, 16, 17) and it should be remembered that the first to propose the nitrous oxide method were rather generous in their estimate of the blood flow (18).

For a few years the ideas of the Oxonians seemed to prevail in this country. The situation was not to last for the Scandinavian school was soon to have a vigorous representative here and one who spoke with no little authority. Grollman's authority was generally accepted because of a vast amount of impressively self consistent work. All of the variability and doubt was swept away. The output was  $2.2 \pm 3$  liters per square meter body surface and all figures that varied from this mean by more than 15% were either pathological or non basal. One could close the book with a sort of satisfied finality.

As a consequence, very few physiologists had the temerity to report figures that exceeded the Procrustean limits set by Grollman. Those that did so either used "notoriously inaccurate methods" or were completely ignored. Their viewpoint was not as completely unreasonable as was supposed because the Grollman method was not the only method that had been checked against the direct Fick procedure (19). Proponents of the ethyl iodide method of Henderson and Haggard, and of the injection method had been satisfied that their methods gave the same results as did the Fick (20, 21). In spite of these facts the opposition to the idea of small basal blood flows—including even that of Henderson—has gradually subsided.

Controversies of this sort are rarely settled. We get over them and whether the recovery is permanent or a temporary remission always remains to be seen. Some phases of the problem seem about to be reopened and for that reason, a brief review of the physiological implications of cardiac output figures and of the manner in which they have been arrived at is in order.

It seems to me that the heart has little to do with its output. Its activity is regulated by reflex connections with pressure receptors and there has been no mechanism described whose function can be said to control the pumping action of the heart in terms of the minute volume or in terms of the stroke volume. Each organ needs more or less blood in accordance with its activity and satisfies these demands by opening or closing its

own arterioles. This it may do by local reflexes, by axone reflexes or more generally in response to the local accumulation of metabolic wastes or to the local development of anoxia. If many organs become active at once and open their arterioles the pressure in the carotid sinus and aorta goes down and the heart is stimulated to increase its pumping. The opposite occurs when the peripheral demand for blood decreases. The heart merely maintains arterial pressure within physiological limits and in doing so supplies the demands of the several organs.

In the past few years evidence has accumulated as to the quantities of blood needed to satisfy these demands. The best evidence relates itself to kidney blood flow. In order to transport diodrast to the kidneys in the quantities secreted in the urine, blood must flow to these organs at the rate of 1.3 l. per minute (22). The blood flow to the brain is considered to be well over 800 cc. per minute (23). The blood flow through the superior mesenteric artery is said to be of the same order as that through one renal artery (24). If we say that the flow through the coeliac and inferior mesenteric arteries collectively equals that to the other renal artery, we can say that the blood flow to the digestive viscera is at least 1.3 l. per min.<sup>1</sup> There is left the skin, skeletal muscles and heart. It is also said that the iliac arteries carry about as much as the renals (24) when the animal is at rest. The proportionate blood flow to the human leg is probably greater than in the dog. The basal blood flow to the extremities is said to be at least 35 cc. per kg. per min. (25, 26) or, assuming 50 kg. of musculo-cutaneous tissue 1800 cc. per min. When these quantities are summated, it is evident that it takes 4.7 l. /min. to supply the kidneys, viscera, brain and hind legs or 5.2 l. /minute to supply the kidneys, brain, viscera, muscles and skin. Levy and Blalock state that in the dog the kidney receives less than  $\frac{1}{5}$  the total blood flow (27). If the 1.3 l. per min. to the human kidney were to be multiplied 5 times it would indicate a total human blood flow of 6.5 l./min.

These data are incomplete and some of them are quantitatively inexact but the suggestion at least, is evident that the 4.1 per min. which is permitted by the Scandinavian school and by Grollman is scarcely enough to supply all the demands of the body.

If the pendulum is about to swing from these small cardiac output figures to larger ones it

<sup>1</sup>Chairman's Note: According to unpublished data obtained by S. E. Bradley, F. J. Ingelfinger, J. P. Bradley and J. Curry, in twenty-one normal subjects, the average figure for hepatic blood flow was 1498 cc./1.73 m<sup>2</sup>.

would be well to evaluate the methods by which the various figures have been obtained.

Cardiac output methods may be classified as volumetric methods and dilution methods. In addition there are many procedures which can best be classified as secondary methods because, in order to be acceptable they must be calibrated against one of the dilution methods. There is usually something a bit vague about the assumptions or calculations that causes the author to bolster his ideas by comparison with another method that carries more conviction. These secondary methods are a bit slippery in that they always give results which check with the comparison method whatever it may be. Thus one observer (28) checks the X-ray method against the injection method and gets stroke volumes well over 80 cc. and another (29) checks the same method against the Grollman method and gets the usual 60 cc. Since Cournand's development of the direct Fick procedure gives different results that will probably gain general acceptance, one wonders how long it will take X-ray kymographers, ballistocardiographers and pulse-pressure enthusiasts to fall into line.

*Volumetric methods* cannot be applied to man. A plethysmograph (cardiometer) must be put over the ventricles and their change in volume measured or else some sort of flow meter must be connected into the aortic stream. Numerous attempts have been made to get at the stroke volume in this manner and much valuable physiological information is to be had by the use of volumetric methods. They tell us what the heart can do under the handicap of an open chest or traumatic surgery. They furnish us with no information as to what the heart does do under more nearly normal conditions.

*Dilution methods* depend upon the establishment of an arteriovenous difference in the concentration of some substance that is diluted in proportion to the size of the blood stream and whose rate of uptake (or output) by the body is known. The arteriovenous difference may be established (1) by an actual analysis of the concentration of the diluted substance in the arterial and mixed venous blood (2) by inferences as to its concentration in arterial blood from the alveolar air and as to its concentration in the mixed venous blood from the composition of rebreathed air and (3) by the assumption that the procedures have left the mixed venous blood free of the substance in question and that it is merely necessary to determine its uptake and its concentration in the arterial blood.

The cardiac output can be determined by the direct Fick procedure, i.e., actual determination of the A V oxygen difference divided into the oxygen consumption only on the assumption

that oxidations take place in the lungs to a negligible extent. This ghost which had been laid many times in the last half of the 1800's was raised again in the 1890's by Christian Bohr who was unable to account for the respiratory exchange by the product of A V difference and cardiac output as measured by the stromuhr (30). The stromuhr did not measure the coronary circulation and Bohr made an allowance. This allowance was too small as was demonstrated by Henriques (31, 32) who used the injection method (see below) to measure the total circulation, including that to the heart. The total circulation times the A V difference did of course, account for the respiratory exchange. The injection method did therefore, at one time, have a strategic value in establishing the fundamental postulates upon which the direct Fick method is based.

Assuming then, that the pulmonary oxidations are negligible, there is no question but that the direct Fick procedure can be used to determine the cardiac output. The details of the procedure and its application will be given by others in this symposium. For our purposes an example will suffice. An individual who consumes 250 cc. of  $O_2$  per minute has a difference between the oxygen content of his arterial and mixed venous blood of 50 cc. per liter. It will therefore, take 5 liters of blood per minute to carry the oxygen to the tissues.

No special time limits handicap the user of this procedure. The mixed venous and arterial tensions do not change while a sample of blood is being taken from the artery or from the right heart. It is far otherwise if a foreign substance is injected into the blood stream or put there by diffusion from breathing a foreign gas. In either case, the arterial concentration must be measured or inferred from alveolar gas tensions and the uptake established during the first circulation. Otherwise it would be impossible to calculate the output from the arterial concentration of the foreign substance because after the first circulation foreign substance would be counted twice. If the lungs are to be used as an aerotonometer to measure mixed venous gas tensions it is again necessary to complete the equilibration before the blood begins to recirculate. If the same blood is exposed twice to abnormal alveolar air, the alveolar gas tension can leave no direct relation to that of the mixed venous blood.

Two questions must therefore be answered in order to evaluate the meaning of rebreathing procedures in determining the cardiac output: (1) What is the total circulation time in man, i.e., how long after a substance appears at a certain point in the circulation will it reappear in significant quantities? and (2) Will this circulation

time be appreciably modified by holding the breath or by active rebreathing procedures?

In answer to the second question, Stewart (33) showed that the circulation time might be  $\frac{1}{2}$  less on inspiratory standstill than during continued respiration. This is attributed to an increase in blood flow to the right heart (i.e. to an increase in cardiac output). The cardiac output is increased in man during the holding of the breath and during other respiratory gymnastics as evidenced by the fact that the Oxygen uptake during such maneuvers is 30-100% greater than it is at rest (1, 8). The oxygen tension of the venous blood returning to the lungs is supposedly unchanged and the only way to account for the increased O<sub>2</sub> uptake during the respiratory gymnastics is to think that the changes in intrathoracic pressure have increased venous return and augmented the pumping action of the heart. It is thus reasonable to suppose that the time of the complete circulation is decreased by a considerable amount as compared with that found in the resting individual.

The circulation time has been measured many times and the results present some scatter (34, 35). The scatter is not so wide in fact as it is in the writings of those who would like to have it long enough to include all the time it takes them to complete a favored rebreathing procedure. It is difficult to find actual determinations in the literature of the circulation time in man from one point in the circulation back again to the same point of more than 20-22 sec. According to Vierordt the jugular to jugular time is 26-29 heart beats or 22-24 sec. and Koch found that the circulation time from the anticubital vein to the anticubital vein was 21 sec. It may be that the circulation time from a foot vein back again to the same place may be 35-40 sec. but such data will not answer the question: how soon and to what extent does the main stream passing through the heart and lungs become contaminated by blood which has already been clear around the circulation? It is first contaminated by blood returning over paths that have short circulation times. It has generally been conceded that the coronary path has a short circulation time. Stewart showed it was 2-3 sec. (36). Now it has been stated (2) that the coronary circulation time is so much shorter than that to any other part of the body that quick return over this path cannot introduce more than a small error in measuring the cardiac output. That the coronary blood is not the only blood which returns quickly will be shown by the following considerations.

The heart and lungs may be perfused by a stream flowing at a rate that is similar to the cardiac output. When a dye is injected into such a stream, its concentration in the aorta shows the following changes: After a few seconds, the dye

appears in samples taken successively every second. The concentration increases and then falls off. During the wash out of dye from the heart and lungs the concentration falls exponentially as indicated by the straight line plot of log concentration against time. This means that during successive constant intervals, the concentration of the dye is reduced by a constant fraction of what it had been just before (79).

If the same injection is made into the natural circulation of man, the dye concentration curve takes the same course up until the time of recirculation. This is clearly marked by a sudden deviation from the straight line of descent brought about by dye coming around a second time. This is illustrated in an injection experiment carried out on a man in basal condition with a heart rate of 60 and a cardiac output of 5.5 l./per min. which is exactly the average of Courand's 13 normal basal males as measured by heart catheterization (46).

The time from the first appearance of the dye until its reappearance is the total circulation time, that is, the time it takes blood to follow the quickest path clear around both the lesser and the greater circulations. In 17 normal basal men, this figure varied from 10 to 18 sec. with a mean of 14.7 sec. (37). We may therefore, expect that recirculation may have occurred in ten seconds, that it has probably occurred in 15 sec. and that it has certainly occurred in 18 sec. These figures must be reduced considerably if any active respiratory effects are being made as a part of an experiment in which the circulation time is of significance.

More important than the time in which blood begins to recirculate is the partition between once circulated and twice circulated blood at various intervals after recirculation begins. At the end of one total circulation time the foreign substance is just beginning to recirculate. In a sample taken  $\frac{1}{4}$  circulation time later  $\frac{1}{2}$  of the foreign substance in the sample would be on its second circulation. In a sample taken after  $1\frac{1}{2}$  circulation times the recirculated substance would be  $\frac{3}{4}$  of the whole.  $1\frac{1}{2}$  circulation times is from 12-21 sec. and  $1\frac{1}{3}$  circulation time is 13-24 sec. These observations are congruent with those of Starr and Collins (38) who showed that surprisingly large amounts of blood recirculated in surprisingly short periods of time and are hopelessly incongruent with the notion that a 5% correction will account for the effects of recirculation up to 20-30 seconds (2).

The fact that the total circulation time is variable and extremely short makes it necessary that a definite plateau be established in the relation between rebreathing time and the CO<sub>2</sub> tension of rebreathed air in each experiment before the tension of rebreathed air can be held to

equal that of mixed venous blood. If rebreathing is too long, the lung air tension is greater than that of normal venous blood because recirculated blood carries back an extra load of CO<sub>2</sub>. If rebreathing is too short, there cannot be time enough for CO<sub>2</sub> to be liberated in sufficient amount to bring the residual air up to the venous tension. In addition to this, enough CO<sub>2</sub> must be liberated from the incoming venous blood to compensate for the CO<sub>2</sub> that must go into the lungs and into the stagnant blood in the lungs to raise the tension

because the CO<sub>2</sub> cannot get out into the venous pulmonary air and a large fraction is carried on in the blood as it passes on through the lungs. Let us assume for argument (see Fig. 1) that the CO<sub>2</sub> partial pressure in 1500 cc. of residual air must be raised from 37 mm. Hg to 45.3 (corresponding to a normal V-A drop from 54 to 50 vol.%) by a blood flow of 100 cc. per sec. This required 16.6 cc. of CO<sub>2</sub> which normally would be forthcoming in a little over 4 sec. If the breath is held in the expiratory position, the rising equilib-

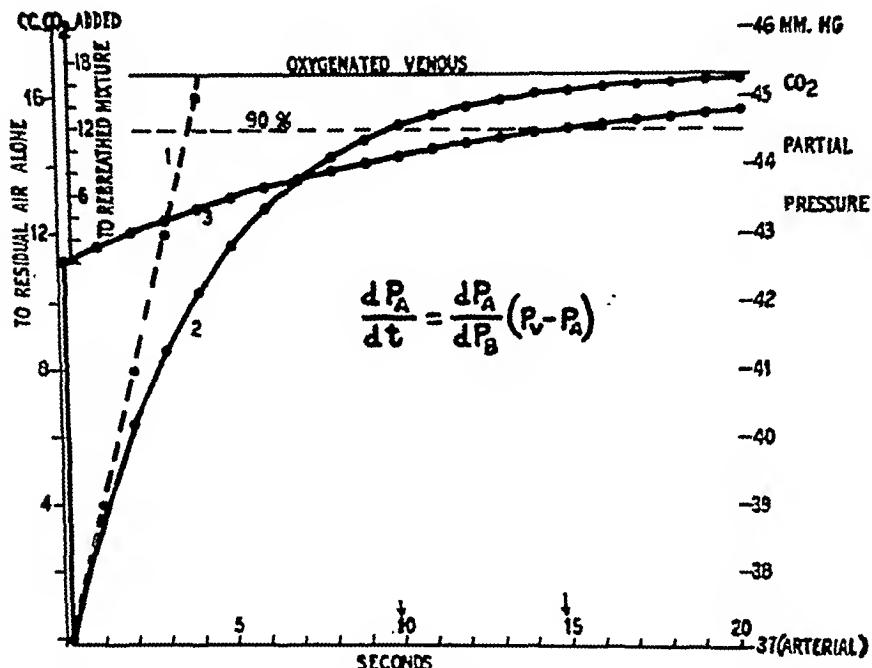


Fig. 1. Calculated curves showing approach of lung air to CO<sub>2</sub> equilibrium with oxygenated venous blood. 1. Normal rate of liberation of CO<sub>2</sub>. 2. CO<sub>2</sub> poured into residual air only. 3. Residual air mixed and rebreathed with twice its volume of O<sub>2</sub> containing CO<sub>2</sub> at venous equilibrium tension. Pv = CO<sub>2</sub> tension in oxygenated venous blood; Pa = CO<sub>2</sub> partial pressure in lung-air and in blood leaving lungs; dPa/dPb = proportionate change in CO<sub>2</sub> tension of lung air and blood caused by exchange of CO<sub>2</sub>. (The assumption of a linear dissociation curve over this short range makes the ratio a constant.) Assumed for calculations: blood flow 6 l. per min.; venous CO<sub>2</sub> 54 vol. % at 43.9 mm. Hg, going to 45.3 mm. Hg on oxygenation; arterial CO<sub>2</sub> 50 vol. % at 37 mm. Hg; residual air 1500 cc; rebreathing mixture 3000 cc. O<sub>2</sub> with CO<sub>2</sub> at 45.3 mm. Hg.

of the pulmonary fluids to the venous levels. The first quantity is some 10-15 cc. and the amount of CO<sub>2</sub> entering the lung fluids may be of the same order (39). The basal rate at which CO<sub>2</sub> is given off is about 3.6 cc. per sec. If CO<sub>2</sub> could be given off at this rate during a rebreathing experiment, it would take 4 to 6 seconds to raise the tension of the lungs and alveolar air to that which might be expected of the venous blood. Of course, the blood can deposit in the lungs but a fraction of the CO<sub>2</sub> which it could if the alveolar tension were normal

rium pressure slows the rate of liberation so that 10 sec. is required to get 90% of the way toward the true venous level. If 3l. of virtual venous air is rebreathed the CO<sub>2</sub> pressure rises rapidly during mixing; but the same volume of CO<sub>2</sub> must still be added to attain equilibrium, and this addition is very slow against the higher tension in the rebreathed air, "90% of equilibrium" now requiring 15 sec. (41).

These considerations indicate that the virtual venous air of the lungs (7) can "never" come into

actual equilibrium with the mixed venous blood though it may come indistinguishably close to such equilibrium in a matter of 12-15 sec. At this time however, the blood is about to recirculate.

When the tension of virtual venous air is plotted against rebreathing time, there is a continuous rise in this tension at the rate of 0.2-0.6 mm. Hg per sec. (39,40). The scatter of the observations is such that to demonstrate a significant lessening of this slope—to say nothing of demonstrating that a plateau exists—rebreathed air samples would have to be taken at least 7 seconds apart and their tensions compared. If the tensions were equal we could say that the slope was significantly less than 0.2 mm. per sec. but not that there was a plateau.

To avoid the diluting effect of residual air on rebreathed air some experimenters have added varying amounts of CO<sub>2</sub> between cycles of rebreathing. This raises the tension got after short rebreathing directly in proportion to the amount of CO<sub>2</sub> added and thus arbitrarily controls the slope of the line correlating virtual venous CO<sub>2</sub> and rebreathing time. It is thus just as easy to get a plateau adding large amounts of CO<sub>2</sub> and rebreathing a long time as it is to get a plateau adding smaller amounts of CO<sub>2</sub> and rebreathing for a shorter time. If CO<sub>2</sub> is added between rebreathings, 3 or more points are necessary to draw a plateau and there are further difficulties in statistically proving that such a plateau actually establishes the mixed venous CO<sub>2</sub> tension.

Some investigators have attempted to gain information simultaneously about the mixed venous O<sub>2</sub> tension and CO<sub>2</sub> tension. The approach is to either get complete equilibrium (14, 15, 16) or to extrapolate to the tensions from the changes in the gases as they are held in the lungs for short periods of time (17, 42, 43, 44). The time necessary to compensate for the dilution of the inspired mixture by the residual air, the consequences of changing the tension of lung tissues and residual pulmonary blood, and the quick return of recirculated blood have not always been fully considered by the experimenters. Thus it is not surprising that some of the above authors report large and some small cardiac outputs and some report both large and small outputs.

In general then, the indirect Fick method gives variable results. The results tend to be low if equilibrium time is long and to be high when the equilibrium time is short. The total circulation time is variable and short so that to be safe the equilibrium time should not be more than ten or twelve seconds (45) if the subject is carrying out rebreathing procedures.

What has been said as to the limits of rebreathing in case of the indirect Fick applies equally to methods based on the uptake of foreign gases by

the pulmonary stream. The dominant one of these methods is that of Grollman. Now Grollman's method gives a figure for the cardiac output which is only about two thirds of that necessary to support the blood flow to the several organs and only about two thirds that found by Courand *et al.* (46) to be the true basal blood flow. Since Grollman's method gives results which are so grossly in error it is not necessary to work over in detail the technics of his method nor the results which numerous workers have had with it and with similar methods. The method involves rebreathing gas mixtures containing acetylene and after 15-18 seconds taking a sample. A second sample is taken 5-8 seconds later, and the cardiac output calculated from the relation between the uptake of acetylene and oxygen during rebreathing on the one hand and the basal oxygen consumption on the other.

It should be pointed out that both the first and the second samples were taken after recirculation had occurred. This is evident from the total circulation times listed above and from the experience of Gladstone (47) who found that the rate of acetylene disappearance suddenly changed after the gas had been in the lungs 10-12 sec. This corroborates the findings of Hamilton, Spradlin, and Saam (37) working with acetylene and those of Israels and Lamb working with CO<sub>2</sub> (45). It also serves to explain the fact that taking samples at 18 and 30 seconds instead of at 18 and 24 seconds after beginning to rebreathe the foreign gas makes little difference in the Grollman figure. In this case too, both samples were taken during rather than before recirculation of blood. The second recirculation may well begin after 30 seconds.

Matthes (48) has shown that when the oxygen saturation of ear blood is measured photometrically, it drops suddenly, remaining in equilibrium with lung air when nitrogen is rebreathed. If it drops to a level plateau, it is said that the saturation during the plateau is that of mixed venous blood. This seems reasonable, but it is hard to find in Matthes data evidence that establishes a plateau before recirculation can well be expected.

*Secondary methods* which have been calibrated against one or more of the respiratory methods discussed above are 1, the x-ray method, 2, the pulse pressure method, and 3, the Ballistocardiographic method.

The x-ray method was tentatively described first by Eyster and Meek (49, 50). They took x-rays of the heart in systole and diastole and calculated the corresponding systolic and diastolic volume by the Bardeen formula (51). The difference was found to be of the order of 70 cc. at rest and 95 cc. during exercise. This allows 35-48 cc. for the stroke volume of each ventricle.

Obviously the x-ray fails to register some of the cardiac movement which is responsible for pumping blood.

The advent of the x-ray kymograph tempted other investigators to investigate this problem. One of these (28) did not call the final result of his calculations "stroke volume" but showed that the "Roentgen Kymographic Index" varied with the stroke volume. The other investigator (29) calculated the systolic and diastolic volumes of the heart from the silhouettes at systole and diastole by a modified Bardéen formula and showed that the difference agreed with acetylene figures for stroke volume. Aside from the fact that the acetylene figures are too small one wonders why a method which, calculated in this manner from the silhouette of the whole heart, does not give the net volume change of the whole heart instead of that of one ventricle.

The answer to this query can be made clear by the following experiment (52). Little pieces of silver wire were sewed to the AV groove and to various parts of the anterior ventricular wall, the chest closed, the dog allowed to recover, and the heart visualized fluoroscopically and photographed. The evidence was clear that during systole, the ventricular wall moves downward toward the stationary apex and that the major pumping movement of the heart is a movement of the AV septum toward the apex. This is of course an observation that was first made by Da Vinci (53) and was confirmed during the 19th century (54). The x-ray kymograph visualizes only changes in the cardiac silhouette and is blind to the movements of the AV septum. Now it may well be that the lateral movements of the x-ray shadow increase and decrease with changes of stroke volume. At present, we are in no position to put them into a formula and come out with the stroke volume.

*The pulse pressure method* has been in the literature since 1904 when Erlanger and Hooker suggested that the output of the heart varies roughly as the product of pulse pressure and pulse rate (55). A third factor enters into this relation and that is the distensibility of the arterial tree since a given pressure rise in a distensible aorta would give a greater uptake (proportional to stroke volume) than in a more rigid aorta.

To evaluate the distensibility of the aorta and its branches recourse is had to the pulse wave velocity. The slower the pulse wave, the more distensible the elastic tube along which the wave is propagated. The original equations of Korteweg (56) and Moens (57) were modified by Bramwell and Hill (58) to calculate the pulse wave velocity ( $V_p$ ) from the rise in pressure  $P$  in mm. Hg corresponding to the rise in volume  $V$  starting from

the initial volume of the tube,  $V$ . The Bramwell Hill formulation is

$$V_p = 0.357 \sqrt{V \Delta P / \Delta V}$$

Now it is easy to find in the literature that this formula, and the original ones from which it is derived gave an approximate idea of the relation between tube distensibility and pulse wave velocity. The correspondence between pulse wave velocity as measured and as calculated from distensibility figures was not very close quantitatively, so we decided to reinvestigate the relation (59).

The pulse wave velocities of a series of dogs were determined at a wide range of diastolic pressures using not only the natural pulse waves but also pulse waves produced by suddenly injecting into the aorta whose branches were tied known quantities of a viscous mixture of Ringer's solution and cellosolve. The natural pulse waves and those made after the death of the animal showed the same relation between velocity and diastolic pressure.

The aortas of these dogs were then cut up into 10 mm. segments and each of these segments stretched laterally by applying a tension that gradually increased from 0 to 1000 grams over 1 minutes time (60). The apparatus gave a plot of the relation between the half circumference of the aorta and tension. These values could be used to calculate the relation between internal pressure and contained volumes and the pressure volume relations could be used, in turn, to give a calculated pulse wave velocity that could be compared with those actually measured before and after the death of the animal.

As a result of many measurements we came to the conclusion that the pulse wave velocity calculation indicates a distensibility that is only about  $\frac{1}{3}$  that actually found to exist in the aorta. Over the range of 70-150 mm. Hg diastolic pressure, the aortic distensibility can be calculated from the measured pulse wave velocity, using the following formula

$$V_p = 0.357 F \sqrt{V \Delta P / \Delta V}$$

where the symbols have the same meaning as above and  $F$  is a factor which has a value of 0.8 in man and between 0.6 and 0.7 in the dog.

The addition of this factor is necessary because when the blood vessel wall is stretched quickly, it is more rigid than when it is stretched slowly. The distensibility under sudden increases in pressure determines the pulse wave velocity whereas the distensibility under sustained increases in pressure determines the aortic uptake and this is closely related to the stroke volume. To work out the qualitative aspects of this question, an appara-

tus was designed to measure optically, increases in length of the half circumference of aortic rings as simultaneously measurable tensions were quickly applied. These quick stretch data were calculated to give pulse wave velocities and it was found that the classical equations without the factor  $F$  could be used to relate initial quick stretch distensibility and pulse wave velocity quantitatively. The factor  $F$  is, therefore, a variable which accounts for the viscous resistance of the arterial wall to quick stretches. It is greater and more variable at low diastolic pressures because here the stretch is resisted mostly by smooth muscle. It is smaller and more constant at higher pressure levels because here the stretch is resisted by connective tissue fibers.

In order to measure the aortic uptake in cc. from the pulse wave velocity it is necessary to know the diastolic capacity of the aorta in cc. Autopsy data are of no value because our measurements, confirming those in the literature (61, 62, 63) show that at diastolic pressures, the aortic capacity is two to four times that derived from autopsy measurement at zero pressure. Whether it is two or four times depends upon the diastolic pressure and the distensibility of the aorta and this is what we are trying to measure.

The only estimate of the diastolic size which does not seem to be purely an assumption (64, 65) is that of Bazett (66). He measured the stroke volume of a series of subjects by the Grollman method and found constants which when multiplied by certain bodily dimensions, and corrected by age factors would give figures for the diastolic aortic size. These figures enabled him to use his pulse wave velocity figures to calculate the aortic uptake during systole and from this the stroke volume. The constants were then adjusted until the final result agreed with Grollman's stroke volume figures. The constants will now have to be revised to take into account the viscosity of the aortic wall and the Cournand stroke volume.

*Ballistocardiography* is the subject of two of the papers of the symposium. I will, therefore, confine my discussion to three points concerning which we have new evidence to offer. Starr's development of the theory of the ballistocardiogram is based on the assumption that Machella's hot wire velocity curve (67) is typical of the velocity pattern in normal man, and remains constant with various stroke volumes. Since the data were taken from a dog whose chest was open and whose heart rate was 240/min., the assumption is questionable.

We have calculated cardiac ejection curves by summing the amount of blood which it takes to distend the aorta at successive levels as the pressure pulse contour develops and as the pulse wave goes down the aorta (68), and adding in quantities

to make up for arteriolar drainage which is said to be proportional to pressure minus 20 mm. Hg (69). The calculations are complex but when completed give a curve which represents the summation of cardiac ejection during systole. They are substantiated by the fact that when the calculation was made from the pressure pulse recorded by Wiggers and Katz (70) simultaneously with a cardiometer curve, agreement between the shape of the calculated ejection curve and that of the cardiometer curve was excellent.

Next an ejection curve was calculated from a normal human pressure pulse recorded from the lower carotid using distensibility figures derived from slowly stretching rings from a normal human aorta and pulse wave velocity figures from rapidly stretching rings from the same aorta. A velocity curve was derived from the ejection curve (Fig. 2). It differed in form from the Machella curve, the velocity peak being much earlier (71).

The data from which the ejection curve was assembled permitted us to calculate a force curve which was roughly a summation of all the forces necessary to accelerate and decelerate blood in the (1) heart, (2) ascending aorta and pulmonary artery, and (3) descending aorta. The blood which is moved and stopped by these forces is the blood necessary to fill successive segments of the aorta and pulmonary artery as the pulse wave advances. In calculating the velocities, accelerations, decelerations and masses to obtain the summed force curve, account was taken of the everchanging aortic diameters during systole and diastole. Details of the calculation are given elsewhere (71).

The force curve plotted as a recoil starts downward immediately with ejection and goes upward again as the column of blood in the heart, ascending aorta, and pulmonary artery is first decelerated. There is a downward thrust caused by the impact of blood in the descending aorta against the peripheral resistance and an upward and downward recoil as the semilunar valves close. In addition, there are the later recoils which are coincident with the aortic standing wave system (72).

Now all of these forces are recoils to blood movement and measure the energies of cardiac ejection. Moreover, they alternate in direction at very frequent intervals. It is therefore, difficult to see how they may be ballistically summated by means of a low frequency recorder as could a single thrust followed by passive after vibrations. This viewpoint is emphasized by the results of recording the movements of the body relative to a low frequency ballistocardiograph and simultaneously of the ballistocardiograph relative to the floor. The ballistocardiograph made a typical low frequency record (73, 74) but the body made a record

like that made on the high frequency ballistocardiograph. Evidently, when a low frequency instrument is used, a great deal of the energy produced in the recoil to blood movements is lost in moving the body about on the bed. Moreover, when the acceleration of body and bed are multi-

forces which should produce the I wave have developed. Moreover, the I wave records only about  $\frac{1}{4}$  the force which we calculate as necessary to eject blood headward. This initial discrepancy in timing and extent is hard to explain. The delay is certainly not due to slow recording because the

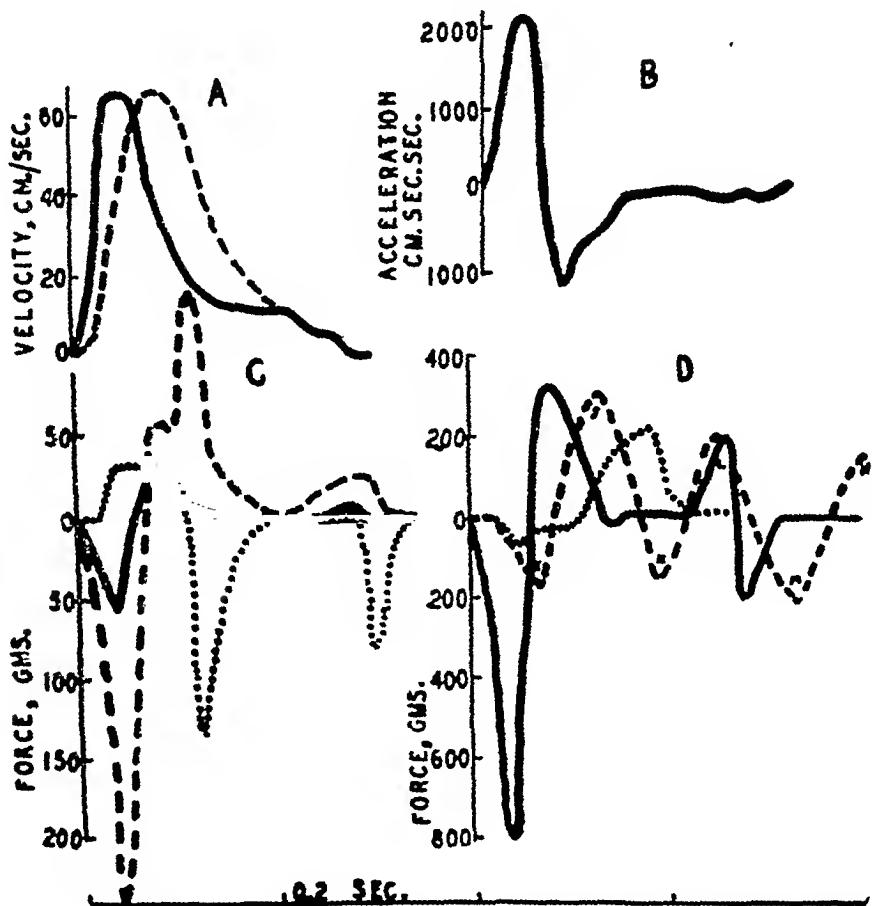


Fig. 2. The construction of a theoretical force picture for the human ballistocardiogram.

(a) Solid line, a velocity curve based on a theoretical human ejection curve. Broken line, a Machella velocity curve, as redrawn by Starr to linear coordinates.

(b) The acceleration curve corresponding to the velocity curve given as the solid line in a.

(c) Derived force curves: Solid line, the cardiac force attendant upon ejection. Broken line, the force representing movement of blood in the ascending aorta. Dotted line, the summated forces representing movement of blood in the three segments of descending aorta.

(d) Solid line, the summarized derived force values. Broken line, the ballistocardiogram given by a high frequency ballistocardiograph (7). Dotted line, the corresponding record from a low frequency ballistocardiograph (7).

plied by their mass with due allowance for damping, the force recorded for the IJ complex is much less with the slow recorder than with the quick recorder.

The I wave of either the high or low frequency ballistocardiogram starts 20 to 30 msec. after the

discrepancy is the same whether the recorder has a high or low frequency. The lag in recording the initial force is not due to slow transmission of stress as through the body because stresses originating outside the body are transmitted through the soft tissues of the abdomen and recorded

The key position of the kidney in the treatment of heart disease has long been recognized. It is beginning to be realized that it plays an important rôle in the cause of congestive failure (85). Salt, which handicaps the kidney in getting rid of water worsens heart disease (86) and mercurial diuretics which poison the reabsorptive functions of the kidney tubules are given almost as a specific treatment for heart disease. The kidney in reabsorbing more water than is needed increases the interstitial fluid volume and pressure and reduces the osmotic tension of proteins in the pericapillary fluids. This leads to edema, to increased blood volume, to increased venous pressure and the chain of events which give rise to the disability of the patient.

The manner in which the kidney is stimulated to undertake this relative increase in reabsorptive function is not clear. The kidney may undergo some intrinsic change that makes it hyperirritable as in nephrosis. More probably it is a response to the pituitary antidiuretic hormone which is known to be secreted during exercise (87) conserving water against future need. The stresses of heart disease simulate those of exercise and may very well induce the excessive secretion of antidiuretic hormone which leads in turn to edema and increased venous pressure.

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## PRESENT STATUS OF THE BALLISTOCARDIOGRAPH AS A MEANS OF MEASURING CARDIAC OUTPUT

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The ballistocardiogram (1) is more than a method of estimating cardiac output, for abnormalities of the size or shape of the record may be used directly to discover abnormalities of the heart and circulation; that is, one does not have to estimate cardiac output to make such a diagnosis in many instances. For this reason research designed to aid in the interpretation of ballistocardiograms has taken two directions.

The first is the empirical approach through experience in the clinic. Thus, after long experience with the healthy had demonstrated the normal form and size of ballistocardiograms, I could cite cases in which abnormal ballistocardiograms were soon followed by the death of the patients, other cases in which changes in the clinical condition were followed by corresponding changes in the normality of the records, other cases in which therapy was followed by improvement in the records, and on the basis of such experience we would slowly learn to interpret ballistocardiograms and so add to our knowledge of the condition of the patients who gave them.

In the early days of the work we were faced

with a difficult decision, whether to report the results obtained by measuring the record, and the normal standards, in absolute units such as dyne-seconds, or in the more familiar units of cardiac output. The fact that so few of my clinical friends had ever heard of a dyne was one of the factors which prompted me to take the bolder, perhaps some will think the rasher, course. But I do not doubt that authors using the empirical method will write many papers on the interpretation of ballistocardiograms without mentioning cardiac output at all.

So it is the second, the theoretical approach to interpretation of the recorded impacts, which concerns us in this symposium. Indeed the problem is so fascinating for those with a moderate knowledge of mathematics that I find it hard to imagine any one pursuing the empirical approach exclusively. I propose, therefore, to spend the rest of the presentation assessing the ballistocardiogram as a method of estimating cardiac output.

*Advantages.* A great advantage is the simplicity of operation from the point of view of both subject and operator. Ballistocardiographs must be

strong and carefully built, but once the apparatus is set up any technician can make the records, and there is no running expense except camera film and developing solutions.

From the subject's point of view the method is ideal, for he has nothing to do except lie relaxed on the table or stand on the platform. Indeed the recording apparatus could be so hidden that the subject did not know that a record was being made. I believe that this absence of disturbing factors is of great importance for the following reasons.

In any quantitative method applied to man there are errors of two types; first, those inherent in the method itself, such as errors of measurement and of analysis; and second, those errors due to changes induced in the subject by the application of the method. Thus certain kinds of emotion are well known to increase cardiac output, and so, any method which might hurt, alarm or disturb a subject, will yield results difficult to interpret. For the changes induced by the emotion will not be predictable, they will vary with the temperament of every subject. Also, they will tend to pass off as the experiment proceeds. I realize that skill in the technical procedures, care in the selection of subjects, their training, and reassurance will do much to minimize this error. Simultaneous measurements of oxygen consumption and pulse rate will help to detect it when present. It will be at a minimum in persons acquainted with laboratory methods and procedure. But in dealing with the general run of patients the interpretation of results secured by a method likely to cause emotion is fraught with the gravest difficulty. I have no hesitation in claiming that the ballistocardiographic procedure avoids the emotional errors far better than any other method now in use.

Ease of operation begets another great advantage, that of multiple estimations. It is too often forgotten that a simple estimate before, and another after a stimulus designed to produce change, gives too little information. Before the significance of a difference can be assessed one must have information about the variability inherent in the method and in the subject; not the variability in the best subjects, but in the subject you are working on, at the very time you are working on him. Duplicate estimations have long been a requirement for chemists, a group of scientists with a long experience with quantitative methods. Physiologists and physicians have more recently emerged from the qualitative view point, and they have been slow to see that multiplicity of estimations is a requirement of many investigations. A simple cardiac output method permits a repetition of estimates which will permit a decision about the significance of differences.

Another advantage is that ballistocardiograms can be taken continuously and so the record permits insight into beat to beat changes in cardiac output and can be used to detect changes of short duration in a way impossible for more elaborate methods.

*Disadvantages.* There are certain difficulties which make us realize that the ballistocardiograph will probably never be a method of the highest precision. We aim to record the performance of one part of a complex dynamic structure. Since it is impossible to connect the instrument to the heart itself, or to adjacent structures, the forces generated by the heart are necessarily distorted in their passage through a long mechanical train consisting of parts of the body, the clothing, the bedding if any, the ballistic table, the pick-up unit and finally the recording device. Each unit of this train will introduce a distortion depending in general upon its natural frequency of vibration and its inherent damping. Ideally each unit should have a natural frequency widely different from the frequency of the activity being observed. While we can approach these ideal conditions in the latter part of the train, the initial part of the train consisting of a portion of the body, which acts as a mass elastically supported, with a high degree of damping, is beyond our control. In most patients the natural frequency of this system appears to be about 6 per second.

These vibrations at approximately 6 per second were believed by Hamilton (4) to be due to blood surging back and forth in the aorta, but the fact that they remain at about the same frequency after death when aortic pressure has fallen, as they were during life, when aortic pressure was present (1) makes me loath to accept this view without reservation. It is true that there is a close correspondence between certain waves in the ballistocardiogram's after-vibrations and waves in pulse records, but one must also recall that after-vibrations may be expected from vibrations of the body mass on its elastic tissue supports.

I believe these 2 sorts of vibrations may be in fact related. Any mass of inert material, containing within its substance fluid encased in an elastic membrane, would have properties which bear on the situation we are discussing. If such a mass is moved, the fluid within it, tending to maintain its position by its inertia, would lag behind until the stretch of its elastic envelope developed sufficient force to move it. So the center of the fluid's mass would be changed in relation to that of the inert material which contained it, and a diminishing back and forth motion of the fluid would be set up until the original situation was restored. So waves would be re-

corded by apparatus anchored in the inert material and recording from the fluid. Similarly, by any movement of the body, waves would be imparted to the blood within it, a fact to be kept in mind by students of the minutiae of pulse wave contour.

However this may be, it has been demonstrated (1) that when known force is applied to the head of cadavers it is distorted in its passage through the body, chiefly by the production of after-vibrations in this period of 6 per second. As the two main ballistic waves, I and J, were but little distorted, we depend on these as our chief guide to the nature of the forces which originated them.

Our newest apparatus has a frequency of about 15 per second, the older ones about 10 per second when loaded with 150 lbs. of rigid weight. The damping of the body is so great that it has not been found necessary to introduce additional damping into the system.

Ideally the frequency of our apparatus should be farther away from the frequency we desire to record. In ballistocardiographs with a slow frequency respiratory movements interfere and the breath must be held before a satisfactory record of cardiac impacts can be obtained. Also the position of the diaphragm at which the breath is held makes a difference to the record, for the impacts are much larger when the diaphragm is held after inspiration than when it is held after expiration, doubtless because the elasticity of the stretched lungs increases the effective filling pressure of the heart. Difficulties such as those have made us prefer ballistocardiographs with a vibration frequency as high as we could make it. But while it is easy to build light apparatus to vibrate rapidly, when the human body must be supported the mechanical problem is much more formidable. Dr. Nickerson has explored the possibilities of low period apparatus more thoroughly than we and will report his experience in the paper to follow this.

The ballistocardiographic method also has limitations of other kinds. To get the best records one must avoid impacts from sources other than the movement of blood. Muscular movements being a major source of interference, the best ballistocardiograms are obtained with the patient lying relaxed. Almost all patients give satisfactory records when lying at rest. Records when the subject stands or sits are satisfactory in a smaller percentage of subjects, as muscular tremors ruin some records obtained from healthy persons and a high percentage when the subjects are sick (2).

As any movement made by the subject may affect the record I see no prospect whatever of estimating cardiac output by the ballistocardiogram during muscular exercise, but on esne

obtain satisfactory records directly after exercise has ceased.

In vigorous breathing the respiratory movements cause impacts which often confuse the record and sometimes render it useless.

Such anatomical abnormalities as mitral valvular disease causing regurgitation, septal defects, patent ductus and coarctation of the aorta may introduce errors although I suspect that they would not be large in most cases.

*Assumptions Used in Calculating Cardiac Output.* The primary assumption is that Newton's laws of motion apply to our problem, and I do not believe that this can be challenged. Therefore the size of the impacts depends on the mass of blood ejected and the rate of change in its velocity.

The main uncertainty is concerned with the shape of the ejection velocity curve. The physiological data on the curve from the left heart are meager (56), and the curve from the right heart, non-existent. To get ourselves started we assumed that a curve obtained by Machella (6) from the aorta of a dog could be applied to both sides of the heart in man. It is the tenuousness of this assumption which makes the estimation from the ballistocardiogram an empirical method.

Now it would be ridiculous to assume a curve of ejection velocity which remained the same at different heart rates. By equating the integral of our curve to the cardiac output we provide for its change of shape at different heart rates. Thus our mathematics (1) assumes that the curve is steep and tall at fast rates, more gradual and flatter at slow rates. All this sounds probable enough, but I call your attention to the fact that it is not based on physiological data. However, by means of this mathematical trick we are in a position to calculate cardiac output and test our results against those obtained by other methods. One can make qualitative comparisons over a large field and quantitative comparisons in a much smaller one.

*Qualitative comparisons.* There is striking accord between our results and expectations about the circulation based on other data. Thus we find a larger circulation in big persons than in small ones, in adults than in children. Food, exercise, excitement and adrenalin (1, 7) increase the cardiac output. Hyperthyroidism is accompanied by an increased cardiac output (8), myxedema by a diminished one (9). All this is exactly what is to be expected and I could greatly prolong the list. This general agreement with expectations based on results obtained by other methods gives powerful support to the general idea under which we are working.

But sometimes our results run contrary to the general view and I will mention one instance to show how the case for a new viewpoint can be

built up even without dependence on the cardiac output measurement. Faintness in the upright position is usually assumed to be due to pooling of blood in the lower parts of the body and lack of venous return to the heart. In a patient with a congenital hemangioma of the leg, in whom I demonstrated that blood did accumulate in this limb when she arose, the cardiac impacts diminished and disappeared before she collapsed (10). But many patients, and also normal subjects given vasodilating drugs (2), have symptoms of dizziness and faintness when their impacts are as large, or even larger, than when they were without symptoms (10). That the symptoms are due to cerebral anemia seems probable enough, but that this was due in turn to dependent pooling and lack of venous return is hard to reconcile with my results. It is conceivable that large impacts could be caused by a small amount of blood ejected at high acceleration, but if this is the situation why did not the patient in whom we know there was pooling show the same phenomenon? So I am thinking of cerebral anemia due to maldistribution of the circulation, rather than to diminished cardiac output, to explain findings such as these.

*Quantitative comparisons.* Quantitative comparisons are available between the ballistocardiographic method and two other cardiac output methods. In our first paper (1) we compared estimates from the ballistocardiogram with results obtained by the improved ethyl iodide method. While in some individual cases the agreement was not very good, the values calculated from the ballistocardiogram agreed with the ethyl iodide results almost as well as duplicates made by the latter method agreed with each other.

Cournand, Ranges and Riley (11) compared ballistocardiographic results with those obtained from the direct Fick method, the development of which was so greatly to their credit. They found that the ballistocardiogram gave results which averaged 18.5% too low and attributed this to an

error in Bazett's method (24) of calculating aortic size which we had employed. When x-ray measurements of aortic size were substituted for the estimation the agreement between ballistocardiogram and Fick results was excellent.

In a later investigation on shock more such comparisons were made. By adding results obtained on patients not in shock to the data mentioned before, corrected according to Cournand's suggestion for the systematic difference or by measurement of the aorta (11), there are 26 comparisons available. In these the ballistocardiograms' results average 1.4% lower than the Fick results. The average deviation from the mean of the two estimates is 2.82% and this can be compared with the corresponding figure for duplicate

estimations made by the Fick method on the same individual. Cournand et al. (13) give this value as 2.6%. Obviously after correcting for the systematic difference the cardiac output as estimated from the ballistocardiogram agrees with that found by the Fick method almost as well as duplicates made by the Fick method agree with one another. No better agreement could be expected.

Systematic differences in cardiac output measurements have plagued workers in this field from the early days of Krogh and Haldane to the present. The difference between average results obtained by the ethyl iodide (14) and acetylene (15) methods on the one hand, and by the Fick method in Cournand's hands (13) on the other, is the modern example. One wonders, of course, whether this systematic difference is not due to the greater emotional tension inherent in the right heart catheterization and arterial puncture which the Fick procedure requires, but if so, it is but little reflected in pulse rate and oxygen consumption, as Cournand et al. (13) have pointed out. Certainly the ballistocardiograph's results contribute nothing to deciding which absolute value is correct for by altering the assumed ejection velocity curve I could make the calculated results agree with either. I have therefore resolved to dodge the issue for the time being by reporting results obtained from the ballistocardiogram, not in absolute values, but in percentage deviation from the average of healthy persons, as is done in estimates of basal metabolic rate. The greatest value of the ballistocardiographic method lies in detecting changes, both changes of cardiac output in single individuals, and deviations from the normal found in the sick; as yet it has contributed nothing towards estimating absolute values.

*Concerning Absolute Values in Cardiac Output Estimations.* I cannot pass a discussion of absolute values without some reflections on the attempts to demonstrate the accuracy of results obtained by cardiac output methods. Years ago we attempted to assess the accuracy of our ethyl iodide procedure by perfusing the isolated lungs of a dog at a known rate while rhythmically inflating them with air containing ethyl iodide, and taking the appropriate samples (16). We obtained satisfactory agreement between the blood flow as calculated from the disappearance of ethyl iodide and the direct measurement, and this might be made the basis of a claim that, since results obtained by the ballistocardiographic method agreed with those secured by ethyl iodide, the ballistocardiographic method gives correct absolute values. But in my opinion such a claim would be completely unjustified, for, when isolated lungs are perfused we avoid some of the chief uncertainties of the ethyl iodide method as applied to man, such as those concerned with the recirculation of

blood. So I make no claim of absolute accuracy for my methods and would not be surprised to find that systematic errors, such as Dr. Cournand believes to be present, truly exist.

On the other hand many persons have accepted the Fick principle as a standard without realizing that there was in the literature a comparison with an absolute measurement which showed that the Fick results averaged much too high. In 1897 Bohr and Henriques (17) reported a study in which the Fick method was applied to dogs while cardiac output was measured by a stromuhr. In a few experiments the results agreed well but in most the Fick values were far too high. The discrepancy was the basis for the idea that there is an active oxygen metabolism in the lungs, a conception that has a few proponents today (18). Compared with modern methods these experiments were crude indeed, but apparently no one has repeated them and found agreement between results obtained by the Fick method and a mechanical method.

Many years ago when working in Dr. Richard's laboratory on eviscerated rabbits I noticed, towards the end of the experiment, that the stream of blue blood ascending the inferior vena cava was joined by a stream of red blood from the renal vein, and that the two columns, instead of mixing, ascended the vena cava side by side until they disappeared from view into the diaphragm. Evidently one has no right to expect the blood in large veins to be completely mixed, so that the assumption that, when blood is drawn from a large vein, the sample represents a perfect mixture of the blood in it, is dangerous indeed. This may well be a major factor in the discrepancy found by Bohr (17), as Zuntz (19) believed; and recently it has been demonstrated by Holt and Knoefel (20) that even blood in the dog's right auricle is not always completely mixed.

On the other hand, confronted with the problem of mixing in experiments published in 1933 (21), we demonstrated to our satisfaction, as had Stewart (22) before us, that blood in the aorta and pulmonary artery of dogs was completely mixed. Obviously, therefore, it becomes mixed as it passes through the heart and I have no doubt that Cournand's newer technique (13) by which the sample is drawn from the heart, rather than from the great veins will result in real improvement in the accuracy of his method. Also the constancy of the results of repeated estimations on the same person, and the agreement of duplicates when samples are taken from more than one place in the right heart and great veins, are most encouraging (13). But I would not have readers think that the field is farther along than it is. We still lack conclusive evidence of the ab-

solute accuracy of results obtained by cardiac output methods.

*Limitations of the Present Cardiac Output Formula.* We have been calculating cardiac output from the following formula:

$$\text{Stroke volume} = 33\sqrt{(2 \int I dt + \int J dt)A\sqrt{C}}$$

when  $\int I dt$  is the area of the I wave of the ballistocardiogram in millimeter seconds, and  $\int J dt$  is the area of the J wave, when the calibration of the instrument is adjusted to that we employ. "A" represents the aortic cross section area and has been estimated for each subject from data compiled by Bazett (24). "C" represents the duration of the cycle in seconds, and is estimated from the pulse rate.

The general character of this formula was derived from our theoretical conceptions (1) and it was our plan to determine its constants by comparing results obtained by it with those secured by the ethyl iodide method which we had been using for several years. It so happened, however, that, using the constants calculated from theory, the results agreed with those secured by the ethyl iodide method, so those constants were allowed to stand without adjustment.

In the first paper on this subject (1) we pointed out that if the form of the ballistocardiogram was abnormal, cardiac output could not be calculated by means of our formulae. Abnormalities of impact form are seen chiefly in advanced heart disease and in three such cases the estimate made from the ballistocardiogram was much smaller than the result obtained by ethyl iodide (1).

Also, in severe shock, Cournand et al. (12) have encountered another discrepancy, for in this condition the cardiac output calculated from the ballistocardiogram was far too large in comparison with the Fick results. I was not unprepared for this finding because of my experience with cases of paroxysmal tachycardia, a condition in which the rapid pulse and low blood pressure have some resemblance to shock. In several such cases the ballistocardiogram suggested that the cardiac output per minute during the attack was considerably higher than when the patient's rhythm was normal, a result very different from those obtained by other cardiac output methods.

The cause of the failure of our formula under these conditions seems evident. It is the penalty we pay for our assumed ejection velocity curve. When the heart is diseased one has the right to believe that ejection "loses its snap", so that maximum velocity occurs not early but late in systole and acceleration is accordingly reduced. The nature of the change in form of the ballistocardiogram supports this conception. Our formula fails because it assumes more acceleration than is present.

Cournand's data (12) indicate trouble in the other direction also. In his cases of extreme shock the pulse rate was very rapid, and the blood pressure extremely low. Obviously there was little pressure to oppose the ejection of blood and under such conditions a cardiac contraction of normal strength would cause a greater acceleration, and so a greater impact, than normal. Also at such very rapid rates the assumed adjustment of the velocity curve for different rates may not hold, the actual acceleration being more rapid than our assumption of it. Indeed Cournand (12) points out that the impact curves were changed in contour, having a sharp initial peak. I agree with his interpretation; under these conditions the ballistocardiogram gives too high values for cardiac output because the actual systolic acceleration of blood exceeds that assumed by our formula.

In addition other types of difficulty may occur when the pulse rate is very rapid, for the after vibrations may persist until the following systole and so augment or interfere with the systolic impacts.

These difficulties at extreme tachycardia raise the question whether the ballistocardiograph method is accurate at more moderate tachycardias. Although no direct comparisons are available at present the results obtained in a large series of cases of hyperthyroidism agree well with those obtained by other cardiac output methods (8). So we have the right to expect that we retain our usual accuracy over the range of pulse rate usually found in the clinic.

*Suggestions for improvement.* I wish to conclude with several suggestions for improving the interpretation of ballistocardiograms. Almost complete preoccupation with war duties has prevented much progress on my part, but the direction that the advance will take, once the war is over, is becoming clearer to me.

The main difficulty with the estimation of cardiac output from the ballistocardiogram lies in the assumed shape of the curve of ejection velocity. So the most immediate question to be answered is: Why assume it at all, why not estimate the ejection velocity curve from the shape of the ballistocardiogram? In early papers we mathematically derived the shape of the normal ballistocardiogram from an assumed ejection velocity curve, so obviously, by reversing the method one could take any ballistocardiogram and derive the ejection velocity curve from it. But the multiple integrations we performed in our original calculations make our method far too laborious for routine use, and a simplification will be essential. I visualize a mathematical solution which would permit changing the constants of the formula in accord with the shape of the impact curve. A start in this direction was made in the

first paper, and if successful it should extend the range of usefulness to include both shock and heart disease and probably improve accuracy all along the line.

From a mathematical analysis only, for I have lacked the opportunity to experiment, I have concluded (23) that the factor representing the aortic cross section area, "A" in my formula is unnecessary, and that its inclusion in the formula was an error. I feel very happy about this for the method used to estimate "A" for any subject was derived from extremely scattered autopsy data (25). So its estimation contained very large errors, as Cournand et al. (11) have demonstrated. Fortunately the calculated cardiac output was effected only by the square root of the errors so the omission of "A" and the incorporation of its average effect into the constants will not greatly effect the published results in most instances. It is true, however, that the use of "A" performed the empirical service of bringing together the average normal values for the different decades of life. Certainly the impacts of young people are larger than those of healthy old persons and with "A" discarded another means must be found to unify the normal standards.

The same type of mathematical reasoning which caused me to discard aortic diameter as a factor, suggests that aortic length would be, and there is no provision for it at present in our formula. I visualize this factor as of small importance in adults, but the first person seriously studying children must do some thinking along this line.

The greatest number of people have asked me why the subject's weight did not appear in our formula. They are visualizing a big man and a small man firing similar guns; obviously the recoil drives the small man further backward. But that is not analogous to our situation, in which movement of the body is restrained by the strong spring. One must think of the big man and the small man firing their guns while leaning back against a wall, in this case the force of the recoil goes through their bodies and into the wall. Their bodies transmit it without moving as a whole and so their weight does not enter into the calculation. I do not think we know that the body moves as a unit from the impacts of the blood. A subject lying on a fixed table with only the soles of his feet in firm contact with the moving foot plate of our ballistocardiograph, gives a ballistocardiogram of the normal form, although it is considerably smaller than we obtain by our usual technique when table and foot plate are rigidly connected. One must recall the behavior of the row of billiard balls in contact, the cue ball strikes one end of the row and only the ball at the other end moves off; the force is transmitted through the mass without moving it.

This line of reasoning applies only to ballistocardiograms with a high degree of restraint, it seems probable that the subject's weight should appear in the formula for low period instruments like that of Dr. Nickerson (3). However, no matter how great the restraint there is always some movement of the body and it is conceivable that a factor related to body weight would improve our results also.

Finally, it is obvious that we need two approaches to the cardiac output problem. The first aims towards a method in which everything is sacrificed to get the highest accuracy possible. The second aims towards a procedure so simple that it will have general utility. When these are attained we can correct the simple method in light of experience with the more complex. Progress in both directions has so exceeded my expectations that it seems reasonable to hope that we will soon be in a position to give real meaning to something about which doctors have talked so much and known so little, valid estimations of the strength or weakness of the hearts of patients who come to their care.

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## THE LOW FREQUENCY, CRITICALLY-DAMPED BALLISTOCARDIOGRAPH<sup>1</sup>

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The purpose of this symposium is to provide an opportunity for the presentation and discussion of the various aspects of cardiac output. In the following paper the author has attempted to present a simplified discussion of the theory underlying the low frequency, critically-damped ballistocardiograph. The views expressed in this discussion are obviously elementary, but such simplification is considered justified in view of the complexity of the problem.

The application of ballistic principles to the measurement of cardiac output offers, if successful, many advantages; for example, the measure-

ment of stroke volume under conditions which involve a minimum of disturbance to the subject, and the continual observation of cardiac output during changing physiological conditions. The values of the cardiac output obtained with the ballistocardiograph on normal subjects are in satisfactory agreement with the values obtained by other methods (1). However, under abnormal conditions such as those found in shock, the ballistocardiograph has in the past, failed to give the correct values for the cardiac output (2). This situation has led to an examination of the physical properties of the ballisticsystem with a view to improving its accuracy. A preliminary investigation (3) involved a survey of the type of ballistic record obtained with systems having a wide range of frequency and damping characteristics.

The present work is a study of the properties

<sup>1</sup> The work described in this paper was done under a contract, recommended by the Committee on Medical Research, between the Office of Scientific Research and Development and Columbia University.

of the ballistocardiograph having one of the specific conditions encountered in the previous survey. The natural frequency chosen for the ballistic bed was 1.5 per second and the damping was adjusted to critical damping for the total load as represented by dead weight. The selection of these conditions represents a reasonable compromise between low and high frequency ballistic systems. Under the conditions of extremely low frequencies, only trained subjects can be used, since the control of respiration is essential. Conversely, in the high frequency range, the effect of resonance becomes excessive and results in the interference of patterns produced by successive heart beats. The conditions chosen here permit the recording of the early events of the impact cycle, i.e., the footward and headward components which involve the full stroke momentum, but minimize the later impacts produced by smaller portions of ejected blood undergoing smaller changes in velocity. This situation provides a reasonable resting period between cycles making possible some increase of heart rate without interference of successive patterns. In considering the conditions selected it should be remembered that the primary objective has been the determination of stroke volume by measurement of the initial impacts. Therefore, the impacts occurring subsequent to the ejection merely confuse the patterns and quite properly can be eliminated or reduced if that can be accomplished without sacrifice of accuracy.

In studying the response of the ballistic system to impressed oscillations the theoretical aspects of the problem have been carried beyond the first approximation in which the system is considered as a simple damped oscillator, to a stage of one more degree of complexity, i.e., two coupled damped oscillators.

The equations required to describe the situation are as follows:

$$(1) \quad m_1 \frac{d^2 x_1}{dt^2} + b_1 \frac{dx_1}{dt} + k_1 x_1 + a(x_1 - x_2) = A_0 \cos w_0 t$$

which represents the subject, and

$$(2) \quad m_2 \frac{d^2 x_2}{dt^2} + b_2 \frac{dx_2}{dt} + k_2 x_2 + a(x_2 - x_1) = 0$$

which represents the bed.

In these equations  $m_1$  and  $m_2$  are the masses of the subject and of the bed respectively,  $b_1$  and  $b_2$  are the damping constants,  $k_1$  and  $k_2$  are the Hooke's law coefficients,  $a$  is the coupling constant between the systems, and  $A_0 \cos w_0 t$  represents one of the force components applied to the subject by the heart. The natural frequency of the bed for the total load ( $m_1 + m_2$ ) is 1.5 cycles per second.

The force constant  $k_2$  is therefore given by  $k_2 = 4\pi^2 f_0^2 (m_1 + m_2)$ . The damping which is critical for the total load, furnishes a value for  $b_2$  from the relationship  $b_2^2 = 4k_2 (m_1 + m_2)$ . The values of the constants  $k_1$ ,  $b_1$  and  $f_1$ , which are for the subject, are based on the estimate that  $f_1$  is approximately 5 cycles per second and that  $b_1$  is about equal to the value for critical damping.

The simultaneous solution of equations (1) and (2) yields a relationship between the amplitude of the bed movement  $A$  and the amplitude  $A_0$  of the movement applied at the heart. This

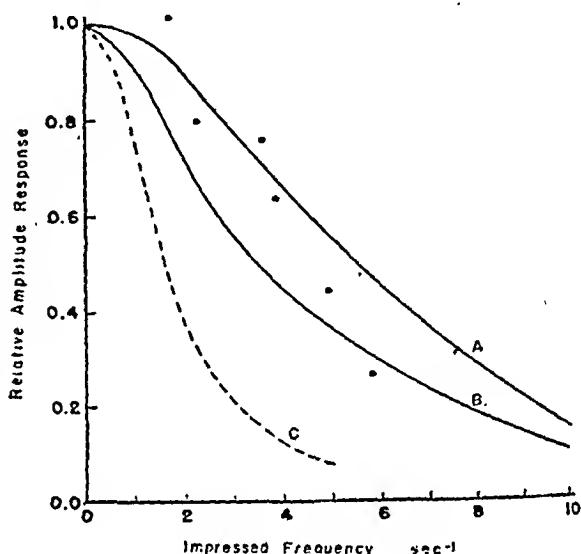


Fig. 1. This figure demonstrates the computed amplitude of response of the coupled system to impressed oscillations of various frequencies. These amplitudes are relative to the value found with the impressed frequency of zero. Curve B is based on the damping constant of the subject taken as the critical value. Curve A is the same with the subject's damping taken as  $\frac{1}{2}$  the critical value. Curve C is the frequency response of a single critically damped oscillator. The dots are experimental points obtained when a mechanical oscillator is applied to the chest of the subject.

is a complicated expression for which numerical values have been computed for several conditions and the results shown graphically in Fig. 1. Curve B is the relative amplitude response curve for the coupled ballistic systems when the damping of the subject is the critical value. Curve A is similar with the damping taken as half the critical value. The dots represent the actual amplitude response to mechanical oscillation applied to the chest of a subject; and the dotted curve shows the response of a single critically damped oscillator. Since the experimental points lie fairly close to the theoretical curves, it is believed that the

equations of motion describing the coupled oscillators give a reasonable representation of the physical conditions in this particular type of ballistocardiograph.

The choice of the uniform physical conditions of frequency and damping for all weights of subjects in the adjustment and use of the ballistocardiograph have made possible a general theoretical approach to the estimate of stroke volume from the dimensions of the ballistic pattern. The value of this uniformity will become apparent as the discussion proceeds. In the present work the records obtained are simply the displacements of the ballistic system during the cardiac cycle. This type of recording is direct and convenient and permits easy calibration.

The procedure followed in calibrating the system is illustrated in Figure 2. A displacing force of

where

$$b^2 = 4(m_1 + m_2)k$$

and

$$k = 4\pi^2 f_0^2 (m_1 + m_2)$$

The general solution of this equation is of the form

$$(4) \quad x = (At + B) e^{-\alpha t}$$

where

$$\alpha = 2\pi f_0$$

Suppose now that the system is at rest and at time  $t = 0$ , it receives an impact giving it a velocity  $U$  in a negative direction (footward). A short time,  $t_1$  seconds later when it has a displacement  $x_1$ , the system receives another impact giving it a

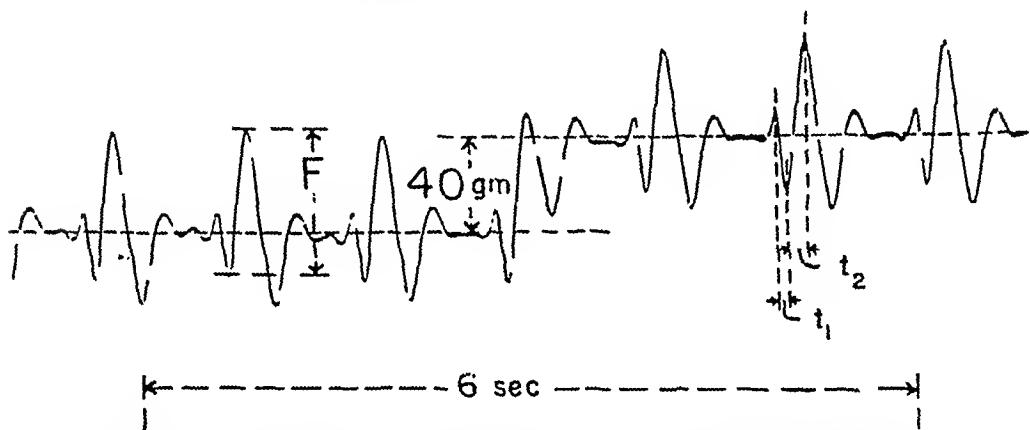


Fig. 2. This figure is a characteristic ballistocardiograph record and demonstrates the method of calibration.

40 grams is applied to the system during the first few heart beats of a record and removed during the next few beats. This produces a deflection of the base line of the pattern by a distance equivalent to the calibrating force. By a simple proportionality it is possible to compute the force,  $F$ , corresponding to the deflection of the pattern between the first major footward and the first major headward movements of each cardiac cycle.

The relationship of this measured force  $F$  to the stroke volume proceeds from the following argument which for convenience is based upon a simpler equation than those presented earlier in this paper. Consider the system as a critically damped oscillator described by the equation

$$(3) \quad (m_1 + m_2) \frac{d^2 x}{dt^2} + b \frac{dx}{dt} + kx = 0$$

velocity  $CU$  in a positive direction (headward). The system reaches its maximum positive deflection  $x_2$  at time  $t_2$  seconds after  $t_1$ .

The overall deflection,  $D$ , of the system during these events is given by

$$(5) \quad D = x_2 - x_1 = Ut_2 \left\{ C - e^{-\alpha t_1} - t_1 e^{-\alpha t_1} \left( -\alpha + \frac{\alpha^2 t_2}{2!} - \frac{\alpha^3 t_2^2}{3!} + \dots \right) \right\}$$

$$(6) \quad \text{or} \quad D = Ut_2 R$$

In this expression  $\alpha = 9.4$  and  $C$ , which is the ratio between the headward and footward impacts has been assigned a value of 1.75. It is possible to measure  $t_1$  and  $t_2$  on the pattern and compute the value of  $R$ . It is obvious that  $C$  is not quite the same for all subjects, but can vary between the limits of 1.37 and 2.00 depending on the elastic

properties of the arterial tree. The value assigned above is satisfactory for most subjects.

The evaluation of the quantity  $C$  proceeds according to the following argument. During the acceleration phase of the systolic ejection the heart as a whole undergoes a footward recoil, a reaction which it communicates to the rest of the ballistic system. Conversely during the deceleration phase of the ejection a headward recoil is

producing the momentum of the ballistic system, then not only the magnitude of the forces but also the duration of their activity must be considered. This of course follows from the principle that the momentum produced by a force is equal to the magnitude of the force multiplied by the length of time during which it acts.

The problem of the headward and footward impulses is not quite as simple as discussed in the preceding paragraph. There are at least two more important impulses active in the system. The first of these impulses is due to the reversal of the blood turning the arch of the aorta. This change of direction effectively doubles the headward momentum contribution of that particular portion of the blood and leads to a value of  $C$  of about 1.37. It should be noted that it does not particularly matter whether this impact is considered to increase the headward impact or to decrease the footward impact. The second impulse is due to the overdistension of the arterial tree on stoppage of the blood going headward. This produces a temporary storage of some of the energy of the blood as potential energy, this energy being quickly retransformed into kinetic energy and the blood given a footward push. This suggests that there is a reversal of direction of movement of considerably more blood than is known to move down the abdominal aorta. The excess of the headward over the footward impacts does not mean that the law of the conservation of momentum is violated, for the balance of the footward momentum appears later either as a second footward swing following  $t_2$  in Fig. 2 or else is neutralized in the premature stoppage of the upward stroke at  $t_2$ .

The time relationships of the displacement and of the velocity of this ballistic system are shown in figure 3. In this illustration when the footward movement has a short duration,  $t_1 = 0.03$  sec., the deflection of the system is 55 units. Similarly when the footward movement is of longer duration,  $t_1 = 0.09$  sec., the deflection is 77 units. By applying now, to each its appropriate correction  $R$ , these become effectively equalized, i.e.,  $55/1.10 = 50$  units and  $77/1.54 = 50$  units respectively. This computation illustrates the effectiveness of equation (6) in determining the correct relationship between  $U$ , the initial impact velocity of the ballistic system, and  $D$ , the displacement of the system.

The force,  $F$ , which is equivalent to the corresponding deflection,  $D$ , is related to it by Hooke's law as expressed in the equation

$$(7) \quad 980 F = 4\pi^2 f_0^2 (m_1 + m_2) D$$

It is therefore possible to determine the velocity of the ballistic bed at the time of the first footward movement by the combining of equations (6) and (7), i.e.,

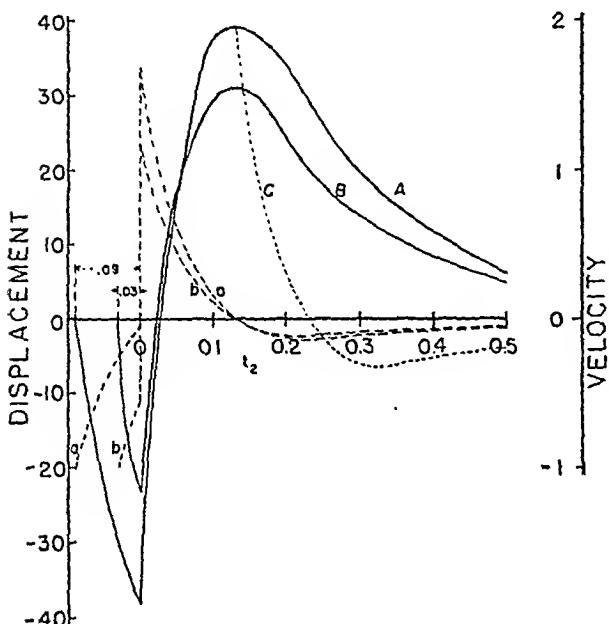


Fig. 3. A diagram showing the displacement and velocity curves for the ballistic system as computed from the equation for the single critically damped oscillator. Curve A represents the displacement of the system when the footward impact velocity  $U$  is followed 0.09 second later by a headward impact of value  $1.75U$ . Curve B is the resulting movement when the same impacts are given to the system, but where the interval  $t_1$  is only 0.03 second. Curves a and b are the corresponding velocity curves. Curve C represents the movement of the system when a footward impact of value  $0.75U$  is given to the system (as represented by curve A) at a time when  $t_2$  equals 0.13 second.

produced. This deceleration is produced not only by a decrease in muscular activity of the heart but also by the increase in pressure against which the ejection is occurring and is therefore dependent upon the dimensions of the ejection space and its elastic properties. If no further impact reactions became operative one could say that these two successive and oppositely directed impulses are equal in magnitude. It should be remembered at this point that if the problem is approached through a consideration of the forces active in

$$(8) \quad U = 11.05 F / (m_1 + m_2) R t_2$$

At the time of this initial footward impact the relationship between,  $m$ , the mass of blood ejected per stroke,  $v$ , the average velocity of ejection,  $(m_1 + m_2)$ , the mass of the ballistic system and  $U$ , the average velocity produced by the impact, is given by the law of conservation of momentum, i.e.

$$(9) \quad mv = (m_1 + m_2) U$$

On substituting in equation (9) the value of  $U$  from equation (8) and assuming that the density of blood is 1.05, the stroke volume is given by

$$(10) \quad S = \frac{m}{1.05} = BF/t_2 Rv$$

It has been considered wiser for the following reasons to determine the numerical constant  $B$  in equation (10) by comparison with the direct Fick rather than to depend on the theoretical figure. First, that while the impact force  $F$  was calibrated against a static force it actually arises in an oscillatory manner from successive, oppositely directed impacts and therefore requires an amplitude response correction factor. Second, the force  $F$  arises from the movement of blood on both sides of the heart and we are assuming that in general the quantity of blood moved and its velocity are identical in both portions.

Several methods of estimating  $v$ , the average velocity of the blood ejected at systole, are evident. The first approach considers that the velocity is related to the stroke volume,  $S$ , the aortic cross-sectional area,  $A$  and the duration of systole,  $T$ , through the equation

$$(11) \quad a = S/AT$$

The equation for stroke volume becomes

$$(12) \quad S = \sqrt{BTFA/Rt_2} \text{ c.c.}$$

which resembles the form of equation used by Starr (1).

A second method assumes that since the blood must be ejected into the aortic tree against an average resistance proportional to the average systolic pressure,  $p_a = (p_e + p_d)/2$ , then its velocity will vary inversely with  $p_a$  or some power thereof. In the present experimental work (4) it has been found that taking  $v$  as inversely proportional to  $\sqrt{p_a}$  is a fairly satisfactory empirical assumption. In this case the equation for the stroke volume is

$$(13) \quad S = 0.029 F \sqrt{p_a}/t_2 \text{ c.c.}$$

where the constant has been determined by empirical calibration with the direct Fick.

The third method of evaluating  $v$  depends on the measurement of the time required for the blood

ejected to travel some measurable distance in the ejection space. The time interval selected was the time from the beginning of the footward movement to the completion of the headward movement, i.e.,  $(t_1 + t_2)$ . The distance involved is related to the length of the pulmonary artery and to the length of the ascending aorta. Specifically it has been assumed to be proportional to  $L$ , the length of the ascending aorta.

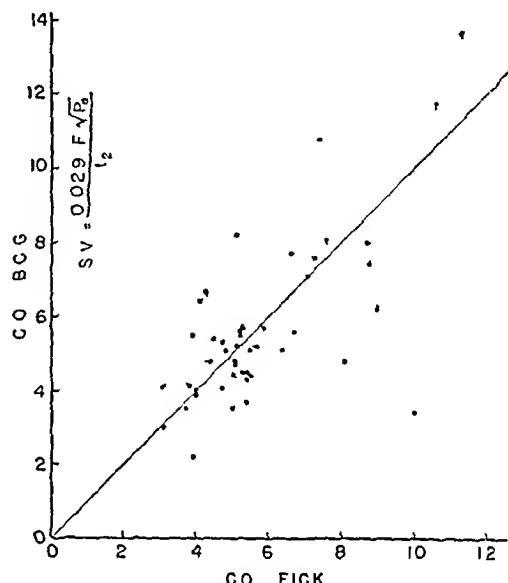


Fig. 4. A comparison of the cardiac output as computed by equation (13) and as measured by the direct Fick method. The small tips on the dots can be used to identify repeated measurements on the same subject under different physiological conditions.

The stroke volume will therefore be given by the equation

$$(14) \quad S = 9.6 F (t_1 + t_2)/RLt_2 \text{ c.c.}$$

where the constant has been determined by empirical calibration with the direct Fick.

Equations (13) and (14) have been used to compute the cardiac output of 47 subjects for whom direct Fick measurements were made at the same time as the ballistic measurements. Since a complete description of this work is in preparation for publication (4), it will be sufficient to demonstrate now the correlation between the computed and measured cardiac outputs. This correlation is shown in Figs. 4 and 5.

The agreement between the computed and measured values is promising. There are however, a few points which are badly out of line. One such point as indicated on Fig. 5 is due probably to an

error in the Fick. Some cases in which the ballistic values are too small illustrate the possibility that the maximum headward swing occurring at the end of the interval  $t_2$  is not attained by a natural development of the movement of the system in that direction, but is rather caused prematurely

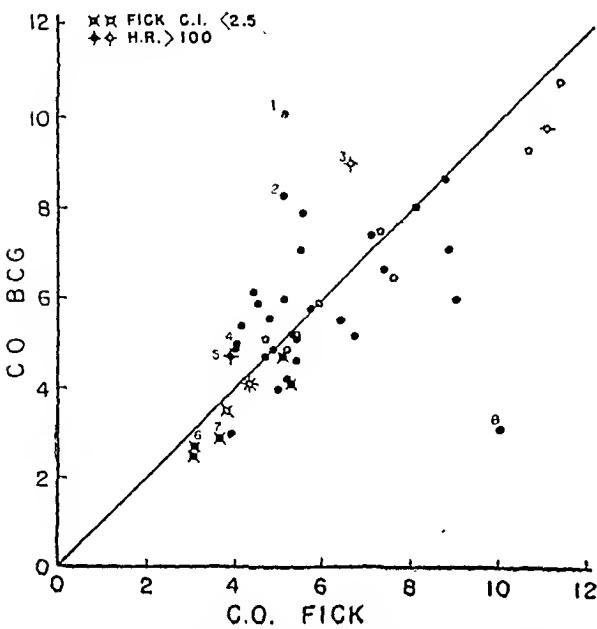


Fig. 5. A comparison of the cardiac output as computed by equation (14) and as measured by the direct Fick method. The solid dots represent those cases for which the aortic length was measured from x-ray plates. The open circles are the cases where  $L$  was considered proportional to the height. The numbers indicate the following special circumstances; 1, stabbed heart; 2, congenital heart disease; 3, mitral stenosis; 4, rheumatic heart disease; 5, paroxysmal tachycardia, heart rate 182; 6, cor pulmonale; 7, A. I. chronic failure; 8, evidence exists for an error in the Fick determination.

by a footward impact, which was discussed earlier in this paper. The computation of a correction for this error is not simple and has not been completed.

The preceding elementary discussion of the origin of the ballistocardiograph pattern and its relationship to the cardiac stroke volume is made possible by the standardization of the ballistic system for all subjects. The assumptions involved, namely, the use of an equivalent impact velocity " $U$ ", instead of the variable velocity known to exist, the use of the quantity " $C$ " as a constant, whereas it is a function of the physical properties of the vascular system, the methods of estimating " $v$ " the mean stroke velocity and the assumption that " $v$ " is the same on the pulmonary as on the aortic side of the circulation, are all simple concepts, yet they combine to give stroke volumes surprisingly close to the measured values. Consequently, a more rigorous investigation of this problem will be attempted.

**CONCLUSIONS AND SUMMARY.** 1. The low frequency critically damped ballistocardiograph has been considered as the equivalent of two coupled damped oscillators. The theoretical relative amplitude response to impressed oscillations is in fair agreement with the experimental response.

2. An elementary theoretical discussion of the relationship between the impacts of the blood during a portion of the cardiac cycle and movements of the ballistocardiograph has been presented.

3. Three equations for estimating stroke volume have been formulated. Two of these equations have been used in the computation of cardiac output for 47 subjects. The agreement between the computed and the measured values is in general promising.

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# MEASUREMENT OF THE CARDIAC OUTPUT IN MAN USING THE RIGHT HEART CATHETERIZATION<sup>1</sup>

## DESCRIPTION OF TECHNIQUE, DISCUSSION OF VALIDITY AND OF PLACE IN THE STUDY OF THE CIRCULATION

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In a short note published in 1870, (1) A. Fick predicated the calculation of cardiac output upon the measurements of O<sub>2</sub> or CO<sub>2</sub> content in the arterial and in the mixed venous blood, and of the total oxygen intake or carbon dioxide elimination by the lungs per unit of time. The two following formulae may therefore be used to calculate the volume of blood flowing through the lungs per unit of time, i.e. the right ventricular output and assuming dynamic equilibrium between both ventricles the result may be extended to determination of the output of the left ventricle:

Cardiac output (mil per min.)

$$(1) \quad = \frac{O_2 \text{ intake (mil per min.)}}{\text{Arterial } O_2 \text{ vol. per cent} - \text{Venous } O_2 \text{ vol. per cent}} \times 100$$

Cardiac output (mil per min.)

$$(2) \quad = \frac{CO_2 \text{ output (mil per min.)}}{\text{Venous } CO_2 \text{ vol. per cent} - \text{Arterial } CO_2 \text{ vol. per cent}} \times 100$$

The practical difficulty which prevented for nearly 60 years the ready application of these formulae to measurement of cardiac output in human subjects has been that of obtaining samples of mixed venous blood. With the development of the technique of catheterization of the right heart this difficulty has been overcome. In 1929, W. Forssman (2) demonstrated on himself, that it was feasible to introduce an x-ray opaque ureteral catheter of very small size, through a large needle into a brachial vein, and by following its progress in the venous system by fluoroscopy to place its distal end into the right auricle. In 1930, O. Klein (3) reported 11 successes in 18 attempts at placing a catheter in the right heart by using the same technique and in 3 cases obtained blood samples for the determination of A. V. O<sub>2</sub> difference. From 1930 to 1939 the technique of right heart

catheterization has been widely used in Europe for injecting contrast substances in order to visualize the right chambers of the heart and the pulmonary vascular tree (4)(5)(6)(7).

During the past 4 years, our group has acquired wide experience with this technique (8), and has developed a method for determining cardiac output in man which can be used in almost all forms of disease and injury and permits repeated measurements over periods of several hours. This method causes no discomfort to the patient beyond that attendant upon the insertion of an indwelling needle in the femoral artery and cutting down a basilic vein for introduction of the catheter in the venous system, both under novocaine anesthesia. It has proven its safety in well over 1,200 cases, not only in ours but in the hands of a number of other investigators in England and in this country. It has become an integral part of a general method of study of the circulation, including intraardiae and arterial pressure measurement and recording, blood volume determinations, respiratory gas exchanges in lung and tissues.

*General considerations concerning technique.* The latest improvements in instrumentation and refinements in the technique of right heart catheterization and femoral artery cannulation have been described in detail in a recent paper (9). They reflect the ingenuity exercised by various members of our team and are the result of much cooperative thinking. Beside promotion of an absolutely safe method, some of our main concerns were: prevention of pain and discomfort, ease of manipulation of the catheter inside the large veins and right heart, and the proper placement of its tip so as to obtain representative sample of mixed venous blood. The development of a catheter opaque to x-rays, still very flexible and provided with a slight curve in its distal 8 cm. was of great help in solving the problem of placing properly and checking easily on the position of the tip of the catheter through the heart's shadow.

In our experience the optimum position is obtained with the tip of the catheter, 1 or 2 cm. above the diaphragm and rotated so as to point medially. Rapid successive samplings in this position and in one of two other positions namely, 3 to 4 cm. nearer to the superior vena cava and nearer to or

<sup>1</sup> The work described in this paper was done under a contract recommended by the Committee on Medical Research, between the Office of Scientific Research and Development and Columbia University. Unpublished data by A. Cournand, R. L. Riley, E. Breed, R. Bloomfield, H. Lauson.

inside the terminal part of the inferior vena cava show sometimes large discrepancies. As a rule the CO<sub>2</sub> and O<sub>2</sub> contents tend to be respectively lower and higher in the sample drawn near the superior vena cava, while the converse is true of the samples drawn from the inferior vena cava. If the tip of the catheter is directed towards the right lateral border of the atrium, contact with the wall may cause intermittent obstruction of the terminal "eye" and prevent easy withdrawal of blood. The samples obtained then may or may not check with samples obtained with the catheter in the optimum position.

Location of the catheter in the optimum position being the first condition of success with this technique, the second is the development of a well trained team, operating smoothly without unnecessary motions and words so as to upset the patient as little as possible, and efficient in collect-

Apparently the validity of the Fick principle cannot be challenged, provided it is admitted *a*, that small inequalities in output of both ventricles are cancelled over a succession of cardiac and respiratory cycles, *b*, that the measured output is actually the effective ventricular output and does not include eventually blood regurgitated through the A-V valves, and *c*, that the oxygen displaced from the inspired air is not utilized in the lung for any other purpose than transport in the circulating blood. The equation derived from the Fick principle is however, correct only if the four related terms, namely: cardiac output, O<sub>2</sub> intake or CO<sub>2</sub> output, arterial and mixed venous blood O<sub>2</sub> or CO<sub>2</sub> content, do not vary in function of time or if their variation around a mean is indeed small. A critical analysis of the method should therefore include an evaluation of the variability of serial measurements, of arterial and mixed venous blood

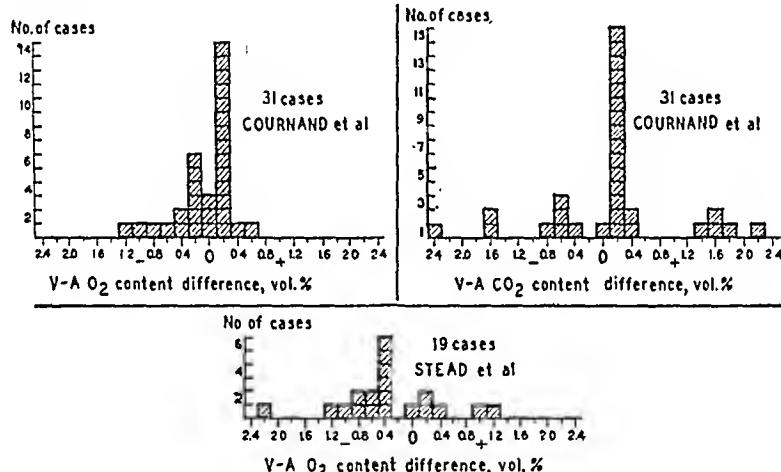


Fig. 1. Frequency distribution diagrams showing O<sub>2</sub> and CO<sub>2</sub> content differences in blood withdrawn successively from right ventricle and auricle.

ing and handling multiple samples and in checking upon many details. With such a team we have been able not only to carry out multiple determinations at very short intervals but to make repeated determinations in cases of severe disease and trauma over periods of time lasting more than 12 hours.

*Validity of the method.* Having solved the problem of sampling simultaneously blood from the right heart and the arterial system, while causing the patient minimal disturbance, it would seem that our only remaining concern would be to estimate the magnitude of the errors involved in the analysis of the samples, in other words determine the limits of technical error in the method.

Contrary to Grollman's statement, to the effect that "The direct Fick method is so direct and unequivocal that the results are open to no possible cavil", closer scrutiny of the problem indicates that a number of questions have to be answered, before accepting the results obtained with the method as representing truly the output of the heart.

gas content and of total O<sub>2</sub> intake or CO<sub>2</sub> output in subjects maintained in a stable state.

The validity of samples withdrawn from the right atrium as representative of true mixed venous blood has been questioned seriously. Evidence has been presented to the effect that in dogs right auricular blood may differ from right ventricular blood in O<sub>2</sub> content (10). No mention is made however, in this work of any control of the position of the catheter in the right auricle by x-ray. It is entirely possible that poor mixing may exist in some areas of the atrium with persistence of stream line flow of blood coming from the superior and inferior vena cava and even from the coronary sinus. If ventricular blood is acceptable as true mixed venous blood, comparison of samples withdrawn successively, in short order from the ventricle and from the auricle or if possible simultaneously is the only means of testing this hypothesis. The frequency distribution diagram seen in figure 1, show separately ventricle-atrial O<sub>2</sub> and CO<sub>2</sub> content difference in samples withdrawn from the

two right heart chambers, in rapid succession (the average time interval being 3 minutes), in 31 cases. The average difference for O<sub>2</sub> and CO<sub>2</sub> content regardless of sign was respectively 0.25 vol. % and 0.63 vol. %. The O<sub>2</sub> content tended to be slightly higher in the auricle than in the ventricle.

TABLE 1

*Variation of carbon dioxide and oxygen content in mixed venous blood sampled simultaneously from the right ventricle and auricle with a double lumen catheter*

SUBJECT	TIME	CARBON DIOXIDE CONTENT		OXYGEN CONTENT	
		Auricle	Ventricle	Auricle	Ventricle
	min:sec.	vol. %	vol. %	vol. %	vol. %
J. K.		49.1	49.5	9.1	9.3
X. Be.		43.4	45.5	17.3	17.1
G. G.		52.7	52.9	8.6	8.8
P. W.		49.1	49.6	14.8	14.8
F. Mc.		43.4	43.9	10.1	10.1
J. Cr.	0		49.8		16.7
	6:00	47.5	45.4	16.4	16.5
	11:00	43.5	47.7	16.5	16.6
A. Po.	0	54.8	54.4	8.5	9.1
	1:00	53.8	54.6	8.1	8.6
F. Ce.	0	49.7	49.7	14.4	13.9
	0:30		49.9		13.7
	2:30		45.9		13.9
	5:00	50.0	50.0	14.4	13.9
M. D.	0	50.5	51.7	16.2	16.2
	1:00	49.6		16.2	
	2:00	49.1		16.4	

TABLE 2  
*Variation in carbon dioxide and oxygen A-V differences in successive samplings*

SAMPLING	TIME INTERVAL	CO <sub>2</sub> CONTENT		O <sub>2</sub> CONTENT		CO <sub>2</sub> V-A DIFF. O <sub>2</sub> A-V DIFF.
		Vol. %	A-Vdiff., vol. %	Vol. %	A-Vdiff., vol. %	
Start collection of expired air . . . . .	0					
Mixed venous blood . . . . .	0:15-0:30	45.8		11.0		
Arterial blood . . . . .	0:30-0:45	41.6	7.0	19.1	-7.2	0.97
Mixed venous blood . . . . .	1:15-1:45	50.1		12.1		
Arterial blood . . . . .	1:30-2:00	43.1	7.0	19.1	7.0	1.00
Mixed venous blood . . . . .	2:35-2:50	49.8		12.1		
Arterial blood . . . . .	2:45-3:00	43.3	6.5	19.3	7.2	0.90
End collection of expired air . . . . .	3:00					

Average CO<sub>2</sub> output = 222 cc./min.

Average O<sub>2</sub> intake = 275 cc./min.

Average R.Q. = 0.81

$$\text{Average } \frac{\text{CO}_2 \text{ V-A Diff.}}{\text{O}_2 \text{ A-V Diff.}} = 0.96$$

cle. This tendency appears more pronounced in the lower histogram, constructed on the basis of data obtained by Stead and his group in 19 cases (11). The spread in the distribution is greater and the difference in O<sub>2</sub> content between ventricle and auricle, regardless of sign, averaged 0.6 vol. %. Why this difference in the two series, is not altogether clear. Among factors which may invalidate such comparative measurements I may

mention *a*, unstable physiological state, *b*, lack of control of the exact position of the catheter in the atrium.

The same arguments of instability or inadequate control of the position in the auricle may not apply to samples withdrawn simultaneously from both chambers of the heart with the help of a double lumen catheter. This catheter specially designed for the purpose of simultaneous sampling and pressure recording at two separate sites of the venous system, in the two chambers of the heart, and even in the pulmonary artery and right ventricle, has two separate lumina, the distal orifices of which are 8 cm. apart. As shown in table 1, of the 9 cases where simultaneous samples were taken from the right ventricle and auricle, the agreement for the O<sub>2</sub> content was excellent in 7 cases and the discrepancies in the remaining two not over 0.5 vol. %. Differences between the CO<sub>2</sub> contents were somewhat greater in a few instances.

The question of the constancy of the arteriovenous difference during collection of expired air, has been studied in a few cases. Experiments of the type exemplified in table 2 should be multiplied. The variation in arterial and mixed venous blood O<sub>2</sub> contents in samples drawn every minute for 3 minutes, are quite small in this case, whereas the variation in CO<sub>2</sub> contents are somewhat larger.

Greater discrepancy between the carbon dioxide contents of ventricular and auricular blood than between the O<sub>2</sub> content, is not unexpected, since slight alterations in respiratory or circulatory

equilibrium change continually the CO<sub>2</sub> content. With ventricular samples, the blood R. Q., i.e.,

$$\text{ratio } \frac{\text{CO}_2 \text{ V. A. difference}}{\text{O}_2 \text{ V. A. difference}}$$

does not check the respiratory gas R.Q. any better than with auricular samples. This requires further investigation and an attempt should be made to

correlate by repeated fractional samplings of blood and expired air, the  $\text{CO}_2$  variations. The arguments that a close check between Blood R.Q. and respiratory gas R.Q. is a good indication of an accurate experimental technique (12) is no longer tenable especially in view of the fact that an excellent check may be obtained with the venous blood sample purposely withdrawn high in the superior vena cava.

Constancy of the  $\text{O}_2$  consumption and of the A-V.  $\text{O}_2$  difference has been further tested in the following manner in 22 subjects (table 3). A first measurement was made not sooner than 30 minutes after the catheter and the arterial needle had been placed; the second measurement was repeated on an average 50 minutes later. All subjects had been fasting for at least 16 hours and were maintained as comfortable as possible in the supine

(2) Occasionally auricular blood may be poorly mixed, indicating persistence of laminar flow in the atrium.

(3) The  $\text{O}_2$  arterio-venous difference, being more constant than the  $\text{CO}_2$  arterio-venous difference, cardiac output should be calculated on the basis of the  $\text{O}_2$  data.

(4) A stable physiological state may be maintained for long periods of time with proper technique, persistent anxiety in most subjects being a negligible factor.

Besides analysis of the constancy of measurements made over short intervals of time, a critical evaluation of any method used to appraise changes in physiological or pathological states should include measurements made on separate dates. Constancy of findings in two normal subjects, studied repeatedly has been reported (9). In one

TABLE 3

*Measurements of  $\text{O}_2$  consumption and  $\text{CO}_2$  arterio-venous difference, repeated at an average time interval of 50 minutes in 22 subjects under basal metabolic conditions*

SUBJECT	$\text{O}_2$ INTAKE CC./M. <sup>2</sup> /B.S.		A. V. $\text{O}_2$ DIFFERENCE VOL. %		SUBJECT	$\text{O}_2$ INTAKE, CC./M. <sup>2</sup> /B.S.		A. V. $\text{O}_2$ DIFFERENCE VOL. %	
	1	2	1	2		1	2	1	2
<b>Normals</b>									
P. McK.	146	149	5.0	5.2	M. K.	167	167	5.0	4.8
L. S.	149	157	4.0	4.2	A. B.	152	150	5.1	5.1
F. K.	96	94	3.9	4.0	G. J.	128	140	4.8	4.9
E. D.	129	124	4.4	4.7	N. K.	142	120	4.6	4.5
Y. C.	116	120	3.3	3.6	V. M.	122	125	5.6	5.5
J. M.	131	128	4.0	4.0	D. M.	133	155	3.0	3.6
J. M.	144	136	4.6	4.3	H. T.	144	160	4.7	4.6
H. W.	135	141	4.5	4.5	A. C.	165	162	4.5	4.2
W. O'B.	158	138	5.6	5.3	J. T.	137	127	5.1	5.3
<b>Cardiacs</b>									
E. S.	142	159	5.5	5.5	J. C.	153	171	4.7	4.5
T. C.	153	141	5.9	6.1	T. D.	155	162	4.1	4.1
E. S.	108	129	6.4	7.0					

position. In the group of 9 normals the  $\text{O}_2$  consumption was well within the normal range of variations of basal metabolism. In the entire group,  $\text{O}_2$  consumption and A-V.  $\text{O}_2$  difference did not vary greatly from one measurement to another. The average deviation from the mean of duplicate measurements of cardiac output, calculated from these data was 2.64% in the group of 9 "normals", 4.21% in the group of chronic pulmonary disease, (including cases of pulmonary fibrosis, emphysema, lung resections), and 3.73% in this entire group, including in addition, 3 cardiacs.

In summary the following tentative conclusions drawn from these comparative studies would seem justified:

(1) True mixed venous blood, may be obtained from the atrium in most instances, provided the catheter is properly placed.

subject, the range of cardiac output per m<sup>2</sup> B. S. in 6 separate determinations made over a period of 5 months, was from 2.85 l./min. to 3.28 l./min., with an average value of 3.09 l./min. In another subject, two measurements of the cardiac output per m<sup>2</sup> B. S. made two years apart were respectively 2.12 l./min. and 2.31 l./min. These studies are still too few and will be extended when circumstances permit.

*Standard values in normal man and quantitative comparisons with other methods.* Measurements of cardiac output were made in a small group of 13 normal healthy individuals (9), at least 16 hours after the last meal, in the recumbent position and approximately  $\frac{1}{2}$  hour after placement of the catheter and the arterial indwelling needle. The flow of saline through the catheter, to prevent clot formation inside its lumen was reduced considerably (approximately 300 cc. for a period of 6 hours)

by addition of a small amount of liquid heparin (1 cc. per 1000 cc.). These normal individuals had been admitted to the hospital or in the clinic for minor complaints. Individuals of this type have been found, as a group, to develop less restlessness and anxiety in the course of the procedure, than other groups of volunteers, such as laboratory assistants, students, physicians and conscientious objectors. Statistics have been calculated in this group and compared to statistics calculated in two groups of normal males, previously reported by Starr and Nylin and studied by the ethyl iodide and acetylene methods. The analysis of significance of difference indicates that the 3 groups were similar so far as concern age, body size, pulse rate and  $O_2$  consumption.

Cardiac output however, by our technique was 3.12 l./min./m<sup>2</sup> of B. S. or 26.8% higher than by either the ethyl iodide or acetylene methods. The oxygen arterio-venous difference by the direct Fick method was correspondingly smaller (4.5 vol. %).

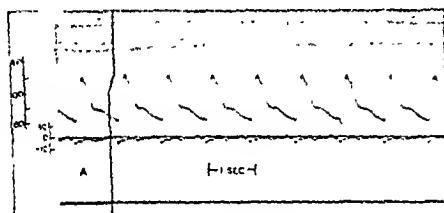


Fig. 2. Simultaneous recording of E. C. G., femoral artery and auricular pressure curves. Vertical line indicates parallax between E. C. G. and pressure curves.

On the subject of comparison of the Direct Fick with the ballistocardiograph (12), I shall comment only briefly. Starr in a previous section of the symposium, has discussed at length the problem of relating forces or displacements as recorded by the ballistocardiograph with stroke volume and stressed the need for improving upon his original formula. If the method of calculation of stroke volume from the ballistocardiograph curves, is open to question, it necessarily follows that the value of comparisons made in the past with the Direct Fick and based on these calculations, is doubtful, however brilliant the rhetoric to defend them. We have therefore filed all our curves until such time when a satisfactory mathematical solution having been found, they may again be calculated in terms of stroke volume.

*Place of the method in the study of the circulation.* The prospects open by the technique of catheterization of the right heart and of cannulation of the femoral artery, transcend the mere measurement of cardiac output. With proper methods of

analysis of blood and expired air samples and use of nomograms it is possible to describe completely the respiratory gas exchange in the lungs and tissues including  $O_2$  saturation,  $pCO_2$ , pHs and alkaline reserve (13). With adequate methods of recording pressures in the femoral artery and in the right auricle and ventricle, (14) valuable informa-

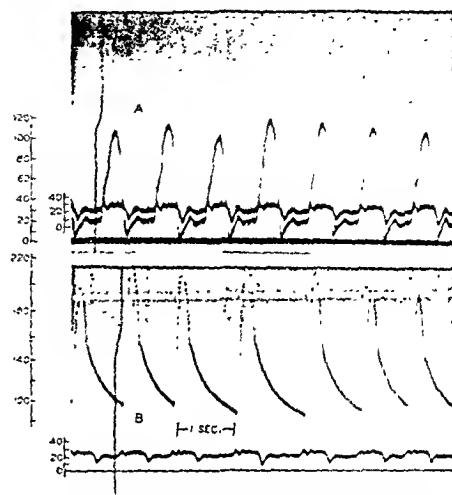


Fig. 3. A. Simultaneous recordings, using a double lumen catheter, of right auricular and right ventricular pressure curves in a case of cardiac failure with tricuspid insufficiency.

B. Simultaneous recordings of femoral artery and right auricle pressure curves in same ease.

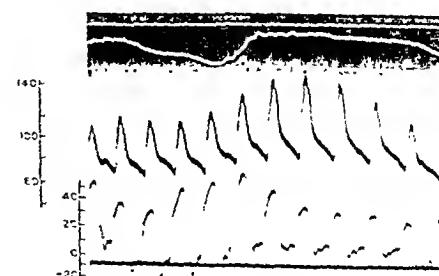


Fig. 4. Simultaneous recording of respiration (downward stroke = inspiration). E. C. G., femoral artery and right ventricular pressure curves.

tion on the dynamics of the circulation may be also gained. Data may then be combined and among some of the resulting physiological functions I may mention the followings as of special interest in studies of physio-pathology of circulation in man. The arterial oxygen transport, a function originally described by Murray and

Morgan, (15) under the name of "Oxyhemoglobin flow", calculated as the product of cardiac output and arterial content. *b*, The ratio of oxygen consumption to the Arterial oxygen transport, a good index to follow oxygen utilization in the tissues. *c*, The mechanical work of the heart, or at least a good estimate of it, which may be calculated as the product of cardiac output, mean arterial pressure and a constant. *d*, Total peripheral resistance, calculated in C. G. S. units as the quotient of the Femoral artery—Right auricular mean pressures difference by the cardiac output.

The technique of simultaneous recordings of pressures curves in the femoral artery, the peripheral veins and the right heart, of electrocardiogram, of respiratory curve and in suitable cases of inter-pleural pressure changes has been considerably improved by two members of our team, Doctors Richard Bloomfield and Henry Lauson. Few such recordings are shown in fig. 2 to fig. 4. It is now possible with suitable membranes and

manometers to obtain in relation with cardiac output measurements, tracings in many instances free from artefacts, showing simultaneous cyclic changes during a succession of heart beats and respiratory motions. From these tracings, pressure variations, pressure gradients, may be calculated and be compared with corresponding stroke volume. From these data information of great interest concerning the intimate mechanics of right heart filling and output may be gained.

In conclusion, I like to point out that the clinical investigator has outgrown the period where measurements of a single physiological entity such as cardiac output was in itself a difficult task. He may hope to contribute in the future to the accumulation of entirely new material to be integrated into the science of hemodynamics, a hunting ground, up to now reserved with few exceptions, to animal physiologists, or physicists without physiological background.

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#### NOTES ON CARDIAC OUTPUT METHODS

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The measurement of cardiac output in man has been a problem fascinating human physiologists and clinicians for the last half-century. Even though methods in the past have given somewhat conflicting and confusing answers, an enormous mass of valuable data on cardiorespiratory problems has been accumulated in the process of technical striving. To the pioneers who struggled so persistently we owe our homage and overwhelming gratitude.

Let us begin at the point we have reached today. The method of cardiac catheterization of

Cournand and Ranges, whereby samples are taken directly from the right heart, will be accepted by all as the most reliable method of determining the denominator of the Fick equation (arteriovenous oxygen difference). The results obtained by Cournand and his colleagues and by us (McMichael and Sharpey-Schafer) indicate that the average arteriovenous oxygen difference at rest recumbent is 45 cc. per liter. With a resting oxygen consumption of 240 cc. per minute this gives an average cardiac output of 5.3 liters per minute. The range, however, is wide, from (240/60) 4 to (240/30)

8 litres per minute. The higher values are obtained mostly in young subjects with some pulse acceleration. There is a significant positive correlation between cardiac output and heart rate. It is difficult therefore, to speak of a "normal" figure for cardiac output. In giving the range (of 4-8 litres. min.) we drew an arbitrary "normal" upper limit to heart rate at 80 beats per minute. The slightest excitement, therefore, will tend to give high values. This influence of rate is also shown in the response of cardiac output to atropine.

The influence of rate change on cardiac output has not always been appreciated. Starling's data on the output of the heart showed that when the rate was accelerated and output remained constant, the venous filling pressure fell.

One very simple cardiac output comparison which has often been made in the past is the effect of change of posture on cardiac output. In 1937, using the acetylene method, I found that the cardiac output increased by an average of 34.5 per cent on changing from the standing to the recumbent position. On a tilting table an increased rate of oxygen intake (+38.5 per cent) in the lungs could also be detected in the first half minute after changing to the supine position, which seemed to agree well with the acetylene data. The catheter method gives an increase of 33 per cent.

While these latter results indicate the value of the acetylene method in establishing general trends of cardiac behavior, we now realize that the average normal value of 4 liters per minute obtained by that method was too low. The reason now seems obvious. Recirculation of blood containing acetylene by short circulation pathways (e.g., coronary) takes place well within the re-breathing period, and gives too low a rate of acetylene uptake in the lungs. Where the cardiac output is low, however, as in the more severe forms of heart failure, the method indicated trends of cardiac behavior (McMichael, 1938) which have been generally confirmed. It is especially significant that the acetylene method did break down most when attempts were made to measure high outputs. It was difficult or impossible to get arterio-venous oxygen differences below 40 cc. per liter by this method. My colleague, Dr. Sharpey-Schafer, has shown that in severe anaemias the arteriovenous oxygen difference is often as low as 20 cc. per liter (C. O. 12 liters/minute). Applying the acetylene method to anaemias in 1938 the lowest figure I could obtain was 38 cc. per liter. I realized that the method was not adequate for this research and abandoned its use for study of rapid circulation.

**Technique: Errors:** The catheter technique was received in Britain with some apprehension in senior circles. The Portuguese and French pioneers in

numbers did not leave the catheter *in situ* more than a few minutes. It is to the everlasting credit of Cournand's group that they established the safety of leaving it *in situ* for a sufficient length of time to make serial observations on cardiac output while various tests and therapeutic measures were carried out. We have fully substantiated the safety of the technique in 353 catheterizations (March 31, 1945). When carried out with all precautions it is without complications other than a little venous thrombosis usually confined to the elbow region. In two subjects in whom we unwittingly used an acid citrate solution thrombosis of the subclavian vein followed. These were our only mishaps. In both subjects the condition completely resolved. The small veins of the arm seem to close down round the catheter, while the high linear velocity of blood flow in the great veins may be a factor precluding clot formation on the unwettable surface of the catheter. We have never used paraffin on the surface. Most of our catheters have been *in situ* for 1-1½ hours, but six have seen left in for 3-6 hours without incident or complication.

The circumstances of our work in wartime have compelled us to carry out our work in the wards. A special room with x-ray equipment is aimed at. A single wet plate, taken while saturated sodium iodide (1-2 cc.) is injected along the catheter, has been our only control on position of the tip. If the tip is not in the middle of the auricle, its position is subsequently adjusted. An occasional wrong turning up into the jugular vein is detected by a "Queckenstedt" test, compressing the jugular veins at the root of the neck and noting whether the citrate solution rises in the manometer. In most instances duplicate samples from the right auricles are in close agreement in their oxygen unsaturation. Every now and again (perhaps in 1 subject in 20) an anomalous sample is obtained, differing significantly from one taken under apparently identical conditions a few minutes previously. Variation in depth of breathing on the part of the subject, with varying oxygenation of arterial blood, accounts for some of them, but in other instances they may represent samples from streams of blood of different composition flowing into the auricle. This was strikingly seen in a case of right subclavian arterio-venous aneurism where some samples obviously contained a gross admixture of arterial blood. In this instance the difficulty of relying on auricular samples was overcome by taking right ventricular samples. It is fortunate, however, that in most instances superior vena caval and inferior vena caval bloods do not differ much in composition and the mixing error is slight. We do not feel that much more is to be gained from accurate localization of the catheter tip as the catheter softens in the warm blood

stream and may change its position somewhat during an observation.

Greater accuracy in the estimation of the arterio-venous oxygen difference is probably achieved by *repeated* arterial sampling from an indwelling needle. We have not used this technique. In subjects whose lungs are normal we have felt that the assumption of 95 per cent saturation of the arterial blood was as good as a single arterial sample the gaseous composition of which would in any case be assumed as constant throughout a series of observations on that individual. When the lungs are abnormal (e.g., emphysema, pulmonary congestion,) an arterial sample is always taken.

*Standards.* Some workers have insisted that cardiac output should be measured in the basal metabolic fasting condition. A development of this has been the expression "cardiac index" or cardiac output per square meter of body surface (normal about 3 liters). We are all aware of the difficulty of getting ideal basal conditions and in certain types of subject they cannot be attained. It has been our habit to make the most of our observations about 2 hours after the midday meal and use whatever oxygen consumption is measured by the spirometer—usually about 240 cc. per minute in the average sized adult. Our figures therefore are actual outputs at the time. Even then we encounter somewhat anxious subjects whose outputs are raised as much as 50 per cent by high oxygen consumption alone (e.g.,  $350/45 = 7.8$  liters).

In making comparative observations in a series of patients (e.g., at various stages of heart failure) troublesome variations arise from varied oxygen consumptions in different sized individuals at different stages of the disease. If it is accepted that the really significant figure is the "resting" arterio-venous oxygen difference, cardiac output can best be expressed as output per 100 cc. oxygen consumed (normal  $100/45 = 2.2$  liters per minute).

For use in clinical investigation, especially of circulatory emergencies, it is obvious that the basal state cannot always be achieved and cardiac index is therefore not entirely satisfactory. The other modes of expression of results also have their limitations. For the moment we must accept

any of these three methods of measurement with an awareness of the drawbacks in each case.

*Right auricular pressure.* The catheter technique allows of considerable accuracy in the measurement of R. A. P. which is a prime factor determining the cardiac output. Cournand and his colleagues take as their zero point the position of the catheter tip as located by lateral x-rays. Unless the catheter position is fairly constant, this has its disadvantages, as a pressure of 2 cm. above the middle of the auricle becomes a pressure of 4 cm. if the catheter is lying along the posterior surface of the auricle. Further, the effective pressure in the auricle is the mean hydrostatic pressure plus the mean negative intrathoracic pressure which cannot conveniently be measured during these observations. Absolute values are thus difficult to define. We have taken for convenience the sternal angle as our zero point following the usage of Lewis' excellent clinical method of observing venous pressure in relation to this level. In the recumbent position the average pressure in the auricle is 4-5 cm. posterior to the level of this point. Respiratory fluctuations in pressure make it impossible to read the manometer with an accuracy greater than  $\pm 0.3$  cm. Owing to this and the slow "settling" of the manometer we do not try to express R. A. P. to a figure more accurate than the nearest  $\frac{1}{2}$  cm. saline.

*Prospects.* The catheter technique allows determination of cardiac output with considerable accuracy. Absolute values of cardiac output and right auricular hydrostatic pressure are difficult to assess and define, but serial observations of pressure and output changes under various physiological tests are yielding results of the utmost value. Anomalous results are rare. It is easily applicable to normal subjects and has yielded results of prime consequence in many pathological states.

The method only measures output when a steady state of the circulation and metabolism can be assumed for a minute or two during which the samples are taken. Thus, when an arterio-venous aneurism is closed off, this state has to be maintained for about two minutes before cardiac output can be determined. We are still lacking a method of proven value to give us the rate of change of cardiac output from beat to beat.

# CARDIAC OUTPUT BY THE CATHETERIZATION TECHNIQUE, IN VARIOUS CLINICAL CONDITIONS<sup>1</sup>

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Even in the short time that right heart catheterization has been used systematically as a technique for physiological study, a considerable amount of information has accumulated, both on normal subjects, and in various forms of injury and disease.

I will give a few examples only, of physiological and pathological changes in the circulation, studied by this technique. Emphasis will be placed on the total circulatory adjustment, as derived from a number of measurements in a given case, rather than the cardiac output values alone.

As Doctor Cournand has indicated, one of the most difficult problems has been that of determining normal resting values of cardiac output and standard conditions.

Like many physiological functions, cardiac output is the resultant of a great number of highly labile factors, physical, vasomotor, and metabolic. Relatively mild disturbances may cause large changes in the output of the heart. This has been known for many years. The more alert and sensitive the individual, the more difficult it has often been to maintain his circulation in a true resting state. One of the early observations in our studies of patients in shock was the evenness and constancy of the cardiac output and other measurements during the state of shock, as contrasted with the patient's over-alert and often restless condition after recovery from his injury.

The establishment of rules for standard basal conditions is somewhat arbitrary, as for any metabolic study. It has been found, however, that it is not enough to have the subject come in from the outside in a fasting state; he must remain in the hospital overnight, before the test. An efficient, smoothly running team is essential, as Doctor Cournand has mentioned. The subject must be made physically comfortable. Since the actual procedure of inserting catheter and arterial needle may be disturbing, even if pain is

prevented, a rest period of at least half an hour should be allowed after completion of the catheterization, before the blood samples are taken. In long experiments, lasting several hours, when repeated cardiac output determinations are made, we have sometimes given small doses of phenobarbital. This lessens restlessness and fatigue and allows the subject to rest or sleep between procedures.

In the thirteen normal male subjects reported by Cournand, Riley, Breed, Baldwin and Richards (1), the resting values for pulse, respiration, ventilation and oxygen consumption were all within normal limits. This suggests that these subjects were as near a standard basal condition as the usual vital measurements can indicate. A further evidence of constancy of metabolic state, in normal subjects, are the repeated measurements in the same individual, reported in the same paper; one subject having had six separate determinations, with all values of cardiac index between 2.85 and 3.28.

On the other hand there are some subjects who are over-alert, anxious, or disturbed, and who do not reach a resting state. Four subjects who had pulse rates or oxygen consumptions above normal were reported by Cournand et al. (1). Cardiac output and pulmonary ventilation were also increased, the former to an average cardiac index of 3.43, as compared with the normal basal value of 3.12.

In general, the experience is not greatly different from that encountered in other metabolic tests, such as that of basal metabolic rate determination. With strict precautions as to preliminary rest and fasting, and with smooth technique, and with the further rest period after the catheter is in place, most subjects will reach a standard resting condition. A few will not, but will be more or less anxious and disturbed during the procedure.

Turning to the response of the cardiac output in certain simple physiological states, we may consider first the still controversial question of the cardiac output in change of posture. McMichael and Sharpey-Schafer (2) have a consistent series of observations in fourteen subjects. All of them showed an increased A-V difference on standing, and a significant average fall in cardiac output. This is in contrast to the conclusions of Grollman (3), using the acetylene

<sup>1</sup>A part of the work reported here was carried out under a contract, recommended by the Committee on Medical Research, between the Office of Scientific Research and Development, and Columbia University, with the collaboration of New York University. Additional support for the research was provided by the Commonwealth Fund and the Josiah Macy, Jr. Foundation.

method, and Starr and Rawson (4) with the ballistocardiograph.

In four experiments carried out in Doctor Cournand's (5) laboratory on the effects on the circulation of breathing under a continuous positive pressure of 20 mm. Hg, the A-V difference was increased by this procedure in all instances. It was not possible to measure oxygen consumption at the same time, but this was done subsequently, showing an increase due to the positive pressure breathing of at most 15 per cent. Cardiac output, calculated by the use of this figure, was significantly decreased during positive pressure breathing, as indicated in table 1.

TABLE 1

*Effect on cardiac output of continuous positive pressure breathing (20 mm. Hg), in four normal subjects at sea level*

SUBJECT	BREATHING PRESSURE	OXYGEN INTAKE	CARDIAC INDEX
			liters
L. E.	mm. Hg	cc./min.	
	0	160	4.98
	+20	(185)	2.99
G. T.	0	167	5.20
	+20	132	3.58
	0	(152)	2.54
G. G.	0	136	4.01
	+20	145	4.07
	0	(167)	2.97
E. R.	0	143	3.49
	+20	130	3.25
	0	(150)	2.28
		124	2.64

Intervals between successive measurements about 30 minutes.

McMichael and Sharpey-Schafer (2) have some interesting data on cardiac output and right auricular pressure following the application of pressure cuffs to the thighs, and following rapid intravenous infusions. They found a close correlation between auricular pressure and cardiac output, indicating that venous return appears under these conditions to control cardiac output. On the other hand, Warren, Brannon, Stead and Merrill (6) have found that, while venous tourniquets produced a fall in auricular pressure, this was not associated with any consistent change in cardiac output. Similarly, transfusions or saline infusions increased auricular pressure but produced no consistent response in cardiac output. The reason for this difference in Stead's and McMichael's findings is not clear.

The response of the circulation to phlebotomy has been given considerable study by the catheterization technique. Warren, Brannon, Stead and Merrill (6) found, as in the case of venous

tourniquets, that right atrial pressure was decreased by phlebotomy, but with no consistent change in cardiac output, whether or not arterial blood pressure fell and the subject fainted. Bareroff, Edholm, McMichael and Sharpey-Schafer (9) studied the effects of phlebotomy in seven cases. Both right auricular pressure and cardiac output fell during the blood letting; but at the end, when the subject actually fainted, the rapid fall in arterial blood pressure and cardiac slowing were not associated with any significant further change in either output or auricular pressure. It was found, however, that blood flow through an extremity, the arm, was increased. From these data the authors deduced that the syncope was associated with a sudden vasodilation in the extremities.

The results in two subjects studied by Cournand are given in table 2. As will be seen, one who received a rapid phlebotomy, had a markedly lowered cardiac output as well as blood pressure; while the second whose blood letting was slower, showed only slight changes.

There are a number of possible forms of compensation, and of failure, following phlebotomy. It seems reasonable to suppose that the total response will vary, both with the individual subject and with the particular phlebotomy procedure used.

The effects of drugs on the circulation in man have been studied extensively by various indirect methods of cardiac output measurement. It may be pointed out, however, that the catheterization technique has two special advantages for the study of rapidly acting drugs: 1, repeated determinations can be made quickly and easily; 2, pathological conditions, including practically all degrees of cardiac and circulatory failure, can be adequately investigated.

The single example which I shall give, the action of methedrine, as described by some experiments by Drs. Cournand, Bloomfield and Lauson (7) is in no sense a complete study of this drug, and is presented largely to emphasize that a drug may act differently in pathological conditions from what it does in normal subjects.

The normal response here, as indicated in table 3, is an increase in arterial blood pressure without change in cardiac output. In the pathological subject J. T., however, the result was quite different. This man had a lacerated scalp and had suffered a mild blood loss. In addition he was acutely aleonolic. This undoubtedly produced a vasodilation which was chiefly responsible for reducing his arterial blood pressure to 63/34. Methedrine in this subject increased markedly both the arterial pressure and the cardiac output, as well as producing an immediate and striking clinical improvement in the patient's general

condition. In the third subject, blood loss without alcohol, cardiac output was unchanged one hour after methedrine. McMichael (8), however, has recorded increase in both arterial pressure and cardiac output after methedrine in subjects who have fainted following phlebotomy.

with low hematocrit, indicating (a) loss of whole blood; (b) compensatory inflow of fluid from normal tissues. The dynamic response is a decreased right auricular pressure, markedly decreased cardiac output, and low arterial pressure. The peripheral resistance (calculated as ratio of mean

TABLE 2  
*Effects of phlebotomy in two normal subjects*

SUBJECT	TIME	PRESSURES (MM. HG)			CARDIAC INDEX	A-V DIFF.	PERIPH. RESIST.	PULSE RATE				
		Arterial (femoral)	Right ventricle									
			Syst.	Diast.								
J. K., normal	0	136/75	22	0	liters	5.3	1870	115				
	Phlebotomy, 655 cc. in 7 minutes											
	10'	46/31	15	2		1.25	9.3	1705	90			
	Gelatin infusion, 800 cc.					2.75	5.6	1530	124			
W. H., normal	0	135/75	34	3	liters	4.0	1260	83				
	Phlebotomy, 1110 cc. in 50 minutes											
	10'	109/60	22	1		3.01	4.8	1140	60			
	Gelatin infusion, 800 cc.					3.50	3.7	1240	66			
122'		136/74	34	1								

TABLE 3  
*Varying effects of methedrine on the circulation*

SUBJECT	TIME	PRESSURES (MM. HG)			CARDIAC INDEX	A-V DIFF.	PERIPH. RESIST.	PULSE RATE				
		Arterial (femoral)	Right ventricle									
			Syst.	Diast.								
F. K., female, 33; normal	0	127/65	25	4	liters	3.9	1760	60				
	0	125/62	21	1		2.34	4.0	1770	58			
	Methedrine, 30 mg. intravenously											
	4'	203/94	43	5		2.64	4.2	2440	62			
J. T., male, 30; lac. scalp, 15% blood loss, acute alcoholism	0	63/34		2	liters	5.0	620	59				
	Methedrine, 30 mg. intravenously (6 hrs. after injury)											
	7'	95/63										
	36'	95/56										
J. K., male, 53; phlebotomy, 20% of blood volume	0	91/50			liters	3.98	700	100				
	Methedrine, 30 mg. intravenously											
	5'	55/37										
	10'	50/30										
	55'	56/55										
		57/56										

In the last three years, Doctor Cournand's group have devoted their primary effort to the measurement of the circulation in shock due to various types of traumatic injury, using the catheterization procedure. More than 100 such cases have now been studied. This work has been described in several papers (10, 11, 12, 13, 14).

In shock due to skeletal trauma or hemorrhage, the marked decrease in blood volume is associated

arterial pressure to cardiac output) is essentially normal. Since blood volume is decreased, the state of the vascular bed, in these forms of shock, is thus one of vasoconstriction. The whole picture conforms to the accepted theory of shock as a form of peripheral circulatory failure, with decreased venous return and decreased blood flow to tissues. A useful index of the extent of failure of tissue circulation, or of the degree of tissue anoxia,

is obtained from the "arterial oxygen transport," or amount of oxygen brought to the tissues per unit of time. This is calculated as arterial oxygen content times cardiac output. It is greatly diminished in cases of trauma with shock (11).

A contrasting hemodynamic response is that occurring in severe burns (10, 13). There is, of course, hemoconcentration rather than hemodilution. There is a considerable amount of blood volume loss and the cardiac output is much reduced. Both the right atrial and the arterial pressures, however, are well maintained.

The peripheral resistance obviously is very high. Hemoconcentration causes increased viscosity, which is a factor. That there is also true arterial vasoconstriction is indicated by the two cases showing the highest values for peripheral resistance. These were studied very early after

Equally important with the diminished blood volume is the behavior of the vascular envelope that encloses it; in other words, the vasomotor tone. In the specific instance of burns just cited, it appears to be not so much a failure of venous return only, as it is a *failure of filling*, of both venous and arterial systems, and of the heart itself.

There are of course many other types and aspects of shock not included in the description just given, each with its own balancing or equilibrium of the forces involved. All, however, involve the phenomenon of a disturbed or diminished circulation operating within an abnormal and usually unstable vascular bed.

In the category of cardiovascular diseases, a reliable method of cardiac output determination, together with the recording of pressures in both

TABLE 4

*Effect of bilateral sympathectomy upon cardiac output and peripheral resistance in five cases of essential hypertension*

	BODY SURF. AREA	MEAN ART. BLOOD PRESS.	CARDIAC OUTPUT			PERIPH. RESIST.	A-V DIFF.	O <sub>2</sub> INTAKE	PULSE RATE
			Per l.	Per minute	Per beat				
		mm. Hg							
Average before operation ...	1.68	160	5.70	3.39	70	2250	41	138	82
Average after operation....	1.60	135	5.52	3.46	64	1960	38	131	87

injury, when plasma loss was still minimal and hematocrit normal (13).

The normal right atrial pressures we at first thought might have been due to pressure bandages around the chest. Subsequent studies have shown that normal or high atrial pressures were found in cases with no bandages. In one recent case, of a severe burn in deep shock, but with normal or elevated arterial pressure, the right atrial pressure remained persistently over 200 mm. H<sub>2</sub>O.

This is clearly not a failure of venous return, in the way that it occurs in shock due to trauma or hemorrhage. It would appear rather to be an extreme vasoconstrictive state involving both arterial and venous systems; perhaps also increased tonus of the myocardium itself.

With a venous pressure as high as 200 mm. H<sub>2</sub>O, one might suspect heart failure, but against this is the prompt and dramatic improvement that follows rapid administration of intravenous fluid, especially plasma or blood, in these cases.

This brief outline will perhaps serve to show that the traditional mechanical concept of oligemic shock, as a simple "failure of venous return," is not adequate to explain the whole picture.

the arterial system, the right auricle, and right ventricle, obviously offers much opportunity for investigation (15).

A study of some interest is that carried out with Dr. Cournand by Docters Chasis, Goldring, Lauson and Riley (16) on five cases of essential hypertension, before and after bilateral sympathectomy. The results are summarized in table 4, as averages for the group. As will be seen, earlier work is confirmed in showing normal values for cardiac output in essential hypertension. A new finding is that sympathectomy caused in these cases no change in cardiac output, its effects being solely that of a moderate reduction in mean arterial blood pressure, and peripheral resistance.

In congestive heart failure, also, the catheterization technique permits an integrated study of cardiodynamics. Table 5 gives the figures in a case of arteriosclerotic heart disease, first in a state of relatively good compensation, and subsequently in advanced decompensation. This case is typical of a considerable number studied both by Dr. Cournand at Bellevue, and by Dr. Baldwin at the Presbyterian Hospital. The changes, as decompensation advances, include: 1, a further drop in cardiac output; 2, increased peripheral

resistance; 3, increased venous pressure with decreased peripheral-central venous pressure gradient; 4, marked rise in right ventricular pressure, and 5, increase in plasma and total blood volumes. In table 6 are given a group of average measurements in rheumatic heart disease with failure, compared with similar measurements in a group of cases of *cor pulmonale*. While the rheumatic cases may have been on the average in a greater

remarkable consistency, both marked arterial oxygen unsaturation and polycythemia. What is cause and what effect in this correlation has not become apparent.

A particular feature that may be illustrated further is that of the central and peripheral venous pressure relations in advanced heart failure. One of the early observations made with the catheterization technique was that in right heart failure, the gradient of pressure from arm to heart drops from a normal average of about 40 mm. H<sub>2</sub>O, to zero (17). More careful studies recently, with the aid of pressure tracings, show that during most of the cardiac cycle, in congestive failure, the central pressure is actually a few millimeters higher than in the peripheral arm vein. Only at the time of initial ventricular contraction and again at the opening of the tricuspid valve, is there a sharp drop in atrial pressure with rapid pouring in of blood from the over-filled great veins. This is described in some detail in a forthcoming paper by Bloomfield, Lauson, Breed and Cournand (18).

Finally, I should like to mention very briefly an excellent study that McMichael and Sharpey-Schafer (19) have made on the action of digitalis.

TABLE 5

*Patient A. R., arteriosclerotic heart disease, hypertension, progressing congestive heart failure*

	DATE	
	9/21/43	1/18/44
Cardiac index (liters) . . . . .	2.33	2.01
Stroke volume (cc.) . . . . .	44	30
Arteriovenous difference (cc./100) . . . . .	5.2	7.4
Arterial blood pressure (mm. Hg) . . . . .	154/80	190/129
Peripheral resistance . . . . .	2570	3335
Auricular pressure (mm. H <sub>2</sub> O) . . . . .	+24	+140
Arm venous pressure (mm. H <sub>2</sub> O) . . . . .	+35	+135
Right ventricular pressure (mm. Hg) . . . . .	27/4	64/18
Plasma volume (cc./sq.m.) . . . . .	1420	1620
Hematocrit . . . . .	40	40
Total blood volume (cc./sq.m.) . . . . .	2370	2700

TABLE 6

*Measurements of the circulation in a group of seven rheumatic heart disease cases, in failure; and in a group of six cases of cor pulmonale, in failure*

	RHEUMATIC		COR PULMONALE	
	Average	Range	Average	Range
Cardiac index (liters)	1.85	(1.21- 2.65)	3.45	(2.59-4.88)
A-V difference (cc./100)	8.1	(6.4-11.4)	4.6	(3.4-5.0)
Peripheral resistance	2562	(1710-3720)	1342	(1100-1510)
Auricular pressure (mm. H <sub>2</sub> O)	+240	(167- 350)	+114	(-24- 180)
Venous pressure (mm. H <sub>2</sub> O)	+245	(173- 320)	+126	(-15- 222)
Ventricular pressure (mm. Hg)	100	(61- 117)	53	(35- 81)
Plasma volume (cc./sq.m.)	2574	(1630-3370)	1655	(1400-1860)
Hematocrit . . . . .	45	(36- 53)	63	(54- 69)
Arterial O <sub>2</sub> saturation (%) . . . . .	95	(90- 98)	71	(61- 85)

degree of failure than those with *cor pulmonale*, this difference was not very great, and the chief variations between the two groups are probably valid. In contrast to the marked depression in cardiac output in rheumatic heart disease with failure, cardiac output tends to be maintained at normal levels in *cor pulmonale*, even in the presence of right heart failure with edema. Both right atrial and right ventricular pressures are relatively higher in the rheumatic group, though considerably elevated in *cor pulmonale*. Blood volume is increased in both, the increase in *cor pulmonale* being almost entirely in the red cells. In this series the cases of *cor pulmonale* with right ventricular hypertension have also had, with

With the catheter in place, they digitalized their subjects rapidly by the use of digoxin, measuring right atrial pressures and cardiac output before and after the drug. They confirmed the finding, already established by other methods, that cardiac output is decreased in normal subjects by digitalization, whereas it is increased in patients with congestive heart failure. In addition, McMichael and Sharpey-Schafer observed in both normal and heart failure groups a sharp drop in right atrial pressure by digitalization. Noting further that these changes are qualitatively the same as can be obtained by mechanical decrease in venous pressure, as by pressure cuffs on the extremities, they suggest that the total action of

may in these cases be on the peripheral vascular bed rather than on the heart itself.

The idea of a single peripheral action of digitalis is an interesting one, and yet I do not think that on this evidence it is demonstrated. The effects of digitalization, in most of the cases presented, are considerably greater, both on pressure and output, than those produced by euffs. Also, as Doctor Dock (20) has pointed out, some of McMichael's cases showed a marked rise in cardiac output after digoxin even though their initial

auricular pressures were scarcely above normal. It would seem more likely that the increased cardiac output was due in part at least to increased myocardial efficiency, the auricular pressure falling as the heart emptied more effectively.

Summarizing very briefly, I have attempted to show in this discussion, by a few examples, how the technique of right heart catheterization can be used to measure cardiac output and other functions in cardiocirculatory disorders.

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## INTERIM REPORT SUBMITTED BY THE SECRETARY OF THE AMERICAN PHYSIOLOGICAL SOCIETY

*Actions of the Council, 1945.* Following the cancellation of the Cleveland meeting, the Council voted to hold a meeting at Rochester, N. Y. on May 18 and 19, 1945 for the discussion of the affairs of the Society. Most of the actions reported below were taken at that meeting.

The following were recommended for election to membership by the Society at its next meeting: H. W. Ades, S. C. Allen, P. B. Armstrong, J. B. Bateman, H. S. Belding, L. L. Bennett, R. V. Brown, B. Campbell, L. D. Carlson, E. Clarke Hay, F. L. Dey, R. L. Driver, H. Goldblatt, R. G. Grenell, R. L. Gregory, H. J. Grindlay, R. A. Groat, F. S. Grodins, Z. Hadidian, W. M. Hart, O. M. Hechter, C. G. Heller, R. Hertz, P. F. A. Hoefer, E. H. Lambert, H. D. Lauson, J. H. Leathem, J. L. Lilienthal, C. A. Maaske, J. E. Markee, F. R. Mautz, W. D. McElroy, J. L. Nickerson, P. A. Nicoll, D. F. Opdyke, W. S. Rehm, Jr., A. Sandow, E. E. Selkurt, R. A. Shipley, R. E. Shipley, R. W. Sperry, H. J. Spoor, E. A. Stead, Jr., W. E. Stone, C. L. Taylor, R. D. Taylor, J. H. Welsh, B. W. Zweifach. Action on twelve other candidates was deferred for another year.

Following the retirement of Dr. W. J. Meek as Chairman of the Board of Publication Trustees, the Council appointed Dr. F. C. Mann to fill this vacancy and Dr. A. C. Ivy was designated to act as Chairman. Dr. Meek has served as Chairman of the Board continuously since it was first organized, and the Secretary was directed to write a letter to Dr. Meek expressing to him the appreciation of the Council and the Society for his valuable services in that capacity.

The Council approved the appointment of Dr. Paul Cannon to the Editorial Board of Physiological Reviews to replace Dr. C. V. Weller who resigned. The report of the Board to the Council was received and accepted. In the annual report of the Board to the Society, it was announced that (1) the \$1000 advanced for the establishment of Federation Proceedings had been returned, (2) that the American Journal of Physiology had a deficit of \$1807.95 for the three volumes of the year, (3) that Physiological Reviews showed a profit of \$3740.95.

The report of the Treasurer was received and approved. The general fund of the Society shows a balance of \$2441.47 on April 1, 1945. The membership dues were set at \$2.50 for the year 1945-46. The President appointed Dr. E. Landis and Dr. E. W. Dempsey to audit the books of the Treasurer.

No applications for the Porter Fellowship were received this year and the Council voted in the future to offer \$2400 in alternate years instead of the usual stipend of \$1200 each year. When Dr. Porter was informed of this decision, he generously offered to increase the payments from the Harvard Apparatus Company in order to enable the Council to offer a fellowship of \$2400 each year. This offer was gratefully accepted.

Further revisions of the Constitution were considered by the Council and will be submitted to the Society in advance of the next meeting so that they can be accepted or rejected at the next business meeting. The Subcommittee on the Constitution consists of Drs. Essex, Mann, and Vischer.

The Council is preparing to recommend a list of candidates for election by the Society as Honorary Members.

Problems of post-war physiology were discussed at some length and a Physiological Survey Committee was appointed under the Chairmanship of Dr. E. F. Adolph. The purpose of the survey is to appraise the present status of physiology and of the Society in this country and to use this as a basis for recommendations for future action.

Dr. Bard, as President of the Society, accepted for the Society the gift of a portrait of Professor Frederic S. Lee of Columbia University and President of the Society 1917-1919. The portrait was donated by the artist, Mr. Cuthbert Lee, of Asheville, North Carolina. Since the Society has no building in which to house such a portrait, it was presented by Dr. Bard to Columbia University.

Plans are going forward for a meeting of the Society in 1946 which will be held unless expressly forbidden by the Office of Defense Transportation.

WALLACE O. FENN, *Secretary*  
*The American Physiological Society*

**PAPER PREPARED FOR PRESENTATION BEFORE THE JOINT SESSION  
OF THE FEDERATION, 1945**

**A POTENTIAL PHYSIOLOGICAL CONTRIBUTION TO THE PREVENTION  
OF "PEPTIC ULCER" IN MAN**

A. C. IVY

*From the Department of Physiology, Northwestern University Medical School, Chicago*

The gastrointestinal autacoids have attracted the interest of physiologists since the discovery of *secretin* by Bayliss and Starling in 1902 (1). Today, the mucosa of the alimentary tract is a close rival of the anterior lobe of the pituitary gland in regard to the number of endocrine principles known to be produced (2). The investigators in this field, like investigators in other fields of endocrinology, have been primarily interested in elucidating physiological mechanisms. However, the possibility that the gastrointestinal autacoids may be diagnostically and therapeutically useful has not been entirely neglected.

The diagnostic use of *histamine*, the physiological action of which is closely identified with the history of the gastrointestinal autacoids, is well known. The use of *secretin* for the more accurate diagnosis of disease of the pancreatic acinar tissue has more recently been shown to be valuable (2-6). It is very probable that *cholccystokinin* will prove to be useful for the diagnosis of functional disorders of the biliary tract (2).

The only gastrointestinal autacoid which now appears to possess potential therapeutic value is *enterogastrone*, or some other agent closely associated with it. It is the purpose of this presentation to provide the evidence upon which such a possibility is based.

**ENTEROGASTRONE.** Enterogastrone refers to a substance or substances present in a fraction of the upper intestinal mucosa which on administration inhibits gastric secretion and motility. It appears to be a true chalone as defined by Sharpey-Shafer (7).

The search for such an agent in the intestinal mucosa started when it was found that a fatty meal, within five minutes after its ingestion, inhibits the motility (8) and secretion (9) of a transplanted pouch of the stomach. It has been found that the introduction of fat or sugar in a concentration of 10 per cent or more by weight or volume into the duodenum will almost immediately inhibit the motility and secretion of a transplanted gastric pouch (10). This does not occur when the fat or sugar is introduced into the stomach and prevented from entering the intestine.

The gastric secretory inhibitory fraction of an acid extract of intestinal mucosa has been concentrated so that an injection of 50 mg. or less

will inhibit the gastric secretory response to 1 mg. of histamine hydrochloride in the dog (11). Two to four times this amount is required in man. The depression of gastric secretion occurs without side reactions such as a change in blood pressure or rectal temperature. The secretion of hydrochloric acid is inhibited considerably more than the secretion of pepsin (12).

**THE PREVENTION OF JEJUNAL ULCER WITH AN ENTEROGASTRONE PREPARATION.** An attempt to prevent the occurrence of post-operative jejunal ulcer in experimental animals by the administration of our enterogastrone preparation was made for two reasons. *First*, it has been well established experimentally and clinically that HCl-pepsin is a factor which is concerned in the extension and chronicity of an ulcer of the stomach, duodenum or jejunum (13). In fact, in man and dog it appears that the secretion of HCl-pepsin is a *sine qua non* for the occurrence of ulcer of the stomach, duodenum or jejunum. We have removed the stomach from more than seventy-five dogs and pigs and anastomosed the jejunum to the esophagus, and have not observed jejunal ulcers to occur during periods extending from one to ten years. Clinically, chronic gastric, duodenal and postoperative jejunal ulcers, other than cancerous, syphilitic and tuberculous ulcers do not occur in the absence of hydrochloric acid secretion; or if they do, they are exceedingly rare. *Second*, it has been observed that patients with an active duodenal ulcer on a diet of milk and cream excrete less of a gastric secretory inhibitory agent in their urine than normal subjects (14). (For a summary of the present status of the antiulcer and gastric inhibitory factors in urine see references 21 and 27.)

**The method for producing "peptic ulcer."** The Mann-Williamson dog (M-W dog) was selected as the most suitable experimental animal for the study. The M-W dog is prepared by performing a gastrojejunostomy and diverting the alkaline pancreatic juice and bile into the last 15 cm. of the small intestine. An ulcer develops in the jejunum where the chyme from the stomach enters.

There are several reasons why we considered the M-W dog the most suitable for our study. *First*, the type of ulcer which occurs is analogous to the ulcer which develops in from 10 to 25 per cent of

human patients after the performance of a gastrojejunostomy. *Second*, it has been demonstrated that acid gastric juice is the chief, though not the only cause of the genesis of the ulcer. *Third*, the ulcer occurs with remarkable consistency. *Fourth*, post-operative jejunal ulcer in man is difficult to manage medically; this is also true of the M-W ulcer, which is not prevented by frequent feedings with or without the usual alkalies (15). And, *fifth*, we are very familiar with the M-W dog and ulcer, because during the past 15 years we have tried by numerous means to prevent or to delay the development of the ulcer. These earlier experiments provide a valuable basis for comparing the efficacy of enterogastrone treatment with other forms of therapy.

The use of the M-W preparation has two disadvantages. *First*, due to the diversion of the pancreatic juice and bile into the last 15 cm. of the small intestine a disturbance of intestinal digestion and absorption is present. To prevent a consequent loss of weight a special diet is given; it consists of par-boiled ground meat, milk, bread, 200 grams each of ground raw liver and pancreas, and some cod liver oil. The animals are offered 800 to 900 grams of the mixture daily. This diet was fed to all dogs in this study. *Second*, when the distal portion of the duodenum is anastomosed to the ileum, the normal position of the intestine is disturbed. This predisposes to intraabdominal herniation with consequent intestinal obstruction. This is the major cause of death in the M-W dog when the occurrence of ulcer is prevented. It is the cause of death in 80 per cent of the dogs which die without an ulcer. The only other important cause of death in the dogs dying without an ulcer is pneumonia secondary to exploratory operations. These are the causes of death in the dogs reported below, dying without an ulcer. These causes of death obtain in our M-W dogs surviving from two months to four years after the initial operation, and must be considered in the interpretation of the results of therapy (15).

**RESULTS. CONTROLS.** *A. Untreated controls.* Ninety-eight per cent of 114 untreated M-W dogs developed ulcer and died 3.8 months (average) after the operation.

*B. Non-specific therapeutic controls.* Ten M-W dogs were treated by daily injections of an extract of hog's muscle prepared by the procedure for making the enterogastrone preparation. All developed ulcer 3.9 months (average) after the operation (16).

*C. Controls for the recurrence of ulcer in M-W dogs.* Ulcer was prevented from developing for 10 months to 1 year in 10 M-W dogs by the three times daily administration of aluminum phosphate gel. Then, this therapy was discontinued. Ulcer developed in all dogs 2.4 months (average) after

discontinuance of the therapy. In two of the dogs the cycle of this therapy with healing of ulcer and the withdrawal of the therapy and recurrence was repeated three times (17). This type of control is important for the interpretation of the results obtained with "enterogastrone" therapy. When aluminum phosphate therapy was discontinued, an ulcer developed in a short time; this is not true of "enterogastrone therapy."

#### RESULTS WITH "ENTEROGASTRONE THERAPY."

*A. Parenteral therapy.* Thirty-three M-W dogs were treated daily and parenterally with the enterogastrone preparation, starting after the operation. The injection caused no rise in rectal temperature during a post-injection period of 5 hours. The treatment was discontinued after one year with the idea that an ulcer would develop, and then the effect of the preparation on healing could be ascertained.

Among this group of 33 animals, 7 or 21 per cent developed an ulcer 6.5 months (average) after the operation and while receiving treatment. Ten died without an ulcer between 2.5 and 12 months after the operation. Nine died without an ulcer from 11 to 31 months after the cessation of treatment. Five are still alive without ulcer, two at 24 months and three at from 40 to 46 months after the cessation of treatment. Two developed ulcer at 18 and 28 months after the cessation of treatment.

Thus, in this group of 33 dogs, the treatment prevented ulcer from developing in 76 per cent of the dogs during a period of one year. Among the 16 dogs, which survived one year, only two (12 per cent) developed an ulcer during a period ranging from 11 to 46 months after the cessation of the treatment.

*Comment.* The fact that most of the dogs did not develop ulcer in the usual time (see Control series C above) after the cessation of this treatment, indicates that the "enterogastrone" preparation caused some long lasting change. The following group of experiments was performed to ascertain if the ulcer could be prevented from developing by treatment for a period of three months.

*B.* Five dogs were injected daily subcutaneously for three months after and five for three months before the M-W operation by Doctor Grossman and Mr. Dutton (18). Among the 10 dogs, 3 developed ulcer in 4 to 6 months; 4 died (2 of pneumonia after devocalization) without ulcer at 15 to 18 months after the operation; and 3 are alive without ulcer 20 months after the cessation of treatment.

*Oral therapy.* Enterogastrone as a concentrate, has not been found to be active in inhibiting gastric secretion or motility when administered orally in doses of 10 or 20 units (19). Nevertheless, it is possible that it may be absorbed by the intestine

when given in larger amounts, or that some substance in the extract other than enterogastrone *per se* is absorbed and is the agent which provides protection against the development of an ulcer. Doctor Grossman with the assistance of Mr. Miller and Dr. Sangster have undertaken experiments to determine the oral effectiveness of crude extracts of the upper intestinal mucosa.

A. The first preparation used was the precipitate obtained by saturating the acid extract obtained by exposure of the intestinal mucosa to 0.4 per cent HCl with sodium chloride (our A precipitate).

Seven M-W dogs after the operation were given 30 grams of the precipitate orally once daily about 6 hours after the last meal. One of these animals developed ulcer 2 months after the operation, and two died without ulcer 5 and 8 months after the operation. The remaining four were free of ulcer 9 months after the operation when the treatment was discontinued. They now are living without an ulcer for from 2 to 4 months after cessation of treatment.

B. To avoid the bulkiness of the sodium chloride precipitate, in which salt is 50 per cent of the solids, the original acid extract has been lyophilized and given orally to 5 M-W dogs. Three grams of this product have been given daily. All of these animals are in good health without ulcer five months after the operation.

**DISCUSSION.** Among 53 M-W dogs receiving parenteral therapy with a preparation of upper intestinal mucosa containing enterogastrone, thirteen or 24 per cent developed ulcer within 6.5 months after the operation, and forty, or 76 per cent did not develop an ulcer during the first year. Twelve of the forty died during the first year without ulcer. Of the remaining twenty-eight, twenty-six have survived without developing ulcer for from 11 to 46 months after the cessation of treatment; two developed ulcer at 18 and 28 months after the cessation of treatment.

Comparing the results on the treated animals with those on the untreated controls, the parenteral therapy reduced the occurrence of ulcer from 98 per cent to 24 per cent during the period of one year. The failure to observe complete protection may be due to three factors. One is that 25 per cent of a series of eight dogs are known to have become refractory to the gastric secretory inhibitory effect of our present enterogastrone preparation (20), when it was given parenterally during a period of several months. The second is that 37 per cent of untreated M-W dogs die of ulcer within 3 months after the operation; hence some substance in the extract other than enterogastrone may not have had sufficient time to affect the 24 per cent which died of ulcer. The third is that the dosage may have been inadequate.

The remarkable aspect of the results is the fail-

ure, in all but two of the animals, to develop ulcer in the usual time after the cessation of treatment. This observation was not anticipated by us. It has been confirmed by Sandweiss and his associates who used an extract of human urine to prevent ulcer in M-W dogs (21).

The mechanism of the long-lasting protection has not been entirely determined. Several possibilities have been considered. (a) It might be due to a physiological adaptation of the jejunum to the operation which occurs with time, provided early death from ulcer is prevented. This is unlikely for two reasons. First, when the development of the ulcer is prevented for one year with aluminum phosphate gel (17), an ulcer develops in 2.4 months (average) after cessation of treatment. Second, two animals developed ulcer 18 and 28 months after the cessation of treatment. (b) It might be due to an abolition of the abnormally prolonged secretion of gastric juice which M-W dogs, like most duodenal ulcer patients, manifest to a meal and to an alcohol test-meal (15, 22-25). M-W dogs treated with enterogastrone for a period of several months do not respond excessively to an alcohol test-meal (26), and pepsin output is not affected (26). Since all M-W dogs do not manifest an excessive response to a test-meal (15) and yet develop ulcer, we doubt that the effect of our present enterogastrone preparation on gastric secretion is sufficient to account for the long lasting protection. For the present, we are inclined to agree with the view of Sandweiss and his associates (21), who explain the protection provided by the injection of a concentrate of human urine as due to an increased resistance of the mucosa to ulceration.

It should be emphasized that one cannot be certain that the active principle in the enterogastrone preparation used is enterogastrone or the gastric secretory inhibitory principle. The agent concerned cannot be considered as a non-specific substance and the protection it provides cannot be considered as being due to a reaction to non-specific protein therapy. This is true for two reasons. First, the extract of hog's muscle provided no protection and non-specific protein therapy is ineffective when the non-specific protein is given orally.

The results on the effectiveness of the oral administration of a crude extract, particularly those obtained with the A precipitate, show that the ulcer preventing agent is active orally. It is too soon to conclude that the lasting protection will result from oral therapy; such a conclusion will be warranted only when the animals have not developed an ulcer when deprived of the therapy for six months.

Whether the occurrence of ulcer in a small percentage of the treated M-W dogs is due to refrac-

toriness, inadequate dosage, or an insufficient period of administration remains to be determined. This may be determined by increasing the oral dose of the crude product and starting its administration three months before the operation.

Whether the results with this therapy on M-W dogs will be applicable to the human patient with peptic ulcer remains to be established. About three years ago we (A. J. Atkinson and H. Greengard) started a small group of so-called "intractable" ulcer patients on parenteral therapy. The preliminary results have been briefly reported elsewhere (18). The results are sufficiently favorable to cause us to continue with the clinical investigation. The knowledge of the oral effectiveness of the crude extract is too recent to have permitted a study on human patients. Several years of investigation are required to establish the effectiveness of any management of peptic ulcer in man because of the natural history of the disease.

If the therapy does not prove to be clinically

effective, it can only be concluded that the ulcer which develops in the M-W dog is etiologically quite different from that which occurs in man. Current opinion and evidence is decisively contrary to such a conclusion.

#### SUMMARY

Evidence from studies on Mann-Williamson dogs, which consistently develop post-operative jejunal ulcer, shows that the daily parenteral administration of an intestinal extract, concentrated in regard to enterogastrone, prevents ulcer from developing in approximately 80 per cent of the dogs. When the therapy is discontinued after several months, the animals are resistant to the occurrence of ulcer for periods of from 18 to 46 months. It has been also demonstrated that a relatively crude extract of intestinal mucosa is orally effective in preventing ulcer in M-W dogs. If these results are applicable to man, hope for the prevention of recurrences of peptic ulcer in man by medical means is well founded.

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*American Society of Biological Chemists***Symposium on the Formation of Disaccharides, Polysaccharides and Nucleosides**CARL F. CORI, *Chairman**Department of Pharmacology, Washington University School of Medicine, St. Louis***INTRODUCTION**

The chief enzymatic reactions which will be discussed in this symposium are listed below.

(1) glucose-1-phosphate + terminal glucose unit (of glycogen)	→ α-1,4 glucosidic chain unit of polysaccharide + phosphate
(2) glucose-1-phosphate + fructose	→ glucose-1-fructose (sucrose) + phosphate
(3) Ribose-1-phosphate + hypoxanthine	→ ribose-1-hypoxanthine + phosphate
(4) glucose-1-fructose + terminal glucose unit (of dextran)	→ 1,6-glucosidic chain unit of polysaccharide + fructose
(5) fructose-2-glucoside + terminal fructose unit (of levan)	→ 2,6-fructosidic chain unit of polysaccharide + glucose

The common feature of the first 3 reactions (going from right to left) is the participation of inorganic phosphate in the splitting of a glycosidic bond with the formation of a 1-phospho-sugar. The process has been called phosphorolysis (in analogy to hydrolysis) and the name "phosphorylase" has been adopted for this class of enzymes. In the reverse direction the 1-phosphorylated sugar reacts with another molecule to form a glycosidic bond while inorganic phosphate is set free. Stated generally, one is dealing with reactions in which there occurs a reversible exchange of an ester bond on carbon atom 1 for a glycosidic bond involving the same carbon atom. The position of the equilibria of the 3 reactions shows that the ΔF is small, of the order of 2000 calories.

The last two reactions, which have been observed in bacteria, consist in the exchange of one type of glycosidic linkage for another, and it is interesting to note that in reaction (4) sucrose acts as a glucoside (analogous to glucose-1-phosphate), while in reaction (5) it acts as a fructoside. In the reverse direction fructose or glucose would play the role of inorganic phosphate in the reactions catalyzed by phosphorylases.

The formation of α- and β-Schärdinger dextrans from starch by *Bacillus macerans* is another example for the exchange of one glucosidic bond for another. One glucosidic bond is broken as a chain of 6 or 7 glucose units is split off and a new glucosidic bond is formed when the open chain is combined head to tail.

The isolation of glucose-1-phosphate, its chemical synthesis and the crystallization of phosphory-

lase from muscle paved the way for a study of the mechanism of reaction (1). The formulation, as given for this reaction, is based on an analysis of the activating effect of added polysaccharide. The non-reducing end groups of the polysaccharide react with glucose-1-phosphate to form a lengthening chain of glucose units. A linear polymer is formed which resembles the amylose fraction of natural starch. Recent advances in the chemistry of starch and glycogen, combined with the information gained from enzymatic synthesis, have given a fairly clear picture of the structure of these polysaccharides.

Reactions (2) and (3) are of great interest; they provide a clue to enzymatic mechanisms which may be involved in the synthesis of other disaccharides and of other ribosides. In these cases there can be no doubt that two different molecules react in the direction to the right. Evidence will be presented that this is also true for reaction (1). The mechanism which is proposed for reactions (4) and (5) and which is patterned after reaction (1) is at present hypothetical; the enzyme preparations obtained so far have not been freed sufficiently of polysaccharide to test the hypothesis. Reactions (4) and (5) provide alternate mechanisms for polysaccharide synthesis in the direction to right and for disaccharide formation in the direction to the left.

With the information now available, which is summarized in this symposium, it should be possible to study the mechanism of formation of many of the polysaccharides which occur in nature, for example that of cellulose. Even an approach to the problem of the enzymatic synthesis of the more complex carbohydrates in pathogenic bacteria would not seem to be out of reach. Such hopes are based on the realization that evolutionary patterns as represented by enzymatic mechanisms repeat themselves in nature in a variety of situations. A sufficient number of cases has been tested to expect that wherever polysaccharides belonging to the starch and glycogen class are found, glucose-1-phosphate will be the substrate from which they are formed. Finally, it is not unreasonable to expect that some of the observations made in the synthesis of one class of substances of large molecular weight, the polysaccharides, will be applicable to other classes.

## RECENT ADVANCES IN THE MOLECULAR CONSTITUTION OF STARCH AND GLYCOGEN

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Starch is generally considered to be the reserve polysaccharide of the plant world, while glycogen is that of the animal world. However, inasmuch as glycogen is found in some lower plants—fungi, yeast, and bacteria—and since a polysaccharide similar to glycogen exists in a higher plant, Golden Bantam sweet corn (*Zea mays*) (1, 2), this characterization is not strictly correct. As we learn more about the chemistry of starch and glycogen it becomes apparent that neither of the two substances is a definite chemical entity and that there is no clear demarcation between them. Starch varies considerably with the source from which it is derived. Waxy maize starch, for example, possesses physical and chemical properties very similar to those of glycogen.

It has now been established that starch is not a homogeneous substance and that it can be separated into two components, amylose and amylopectin, each having a different chemical constitution. The amylose consists of long unbranched chains of about 300 glucose units, while the amylopectin consists of branched chains of approximately 25 glucose units per branch. Unlike starch, glycogen is homogeneous in the sense that it consists only of branched chains. However, its chain length is not always constant. While the branches of glycogens isolated from animal tissues consist of 12 glucose units, it has been found that glycogen isolated from the liver of animals fed galactose or sucrose prior to isolation of the polysaccharide contains chains of 18 glucose units (3). This chain length approaches that of the branches of amylopectin.

The most important structural feature common to starch and glycogen is the  $\alpha$ -1,4-glucosidic linkage. This linkage is responsible for the similarity in specific rotation which starches and glycogens or their derivatives exhibit when dissolved in the same solvents. The similarity in biochemical and physiological behavior of starch and glycogen may also be attributed to the fact that these polysaccharides possess this common structural characteristic. Glycogen is attacked by the same plant amylases that attack starch, and like starch is degraded to maltose and dextrans. Both glycogen and starch are broken down by animal or plant phosphorylase in the presence of inorganic phosphate with the production of glucose-1-phosphate.

### *Various views on the structure of starch and glycogen*

Haworth and Hirst have shown that the starch molecule consists of chains made up of  $\alpha$ -gluco-

pyranose units joined by glucosidic linkages through the first carbon atom (reducing group) and the fourth carbon atom of the next glucose unit through the sharing of an oxygen atom (4, 5). The linkage between any pair of hexose units in the starch chain is the same as in the disaccharide, maltose.

These authors have demonstrated that when starch is repeatedly treated with dimethyl sulphate and alkali, all the hydroxyl groups are replaced by methoxyl groups, producing a methylated derivative which is soluble in certain organic solvents and has a characteristic specific rotation. Hydrolysis of the methylated starch with acid produces 2,3,6-trimethylglucose, together with a small proportion of 2,3,4,6-tetramethylglucose. If the glucoside members in starch are linked together to form a chain of finite length (Fig. 1), the two terminal glucose units of the chain differ in constitution from the intermediate members of the chain and are distinguishable by means of their methyl derivatives. The first, the "reducing" end-group (A in Fig. 1) yields on hydrolysis 2,3,6-trimethylglucose, since the methoxyl group on carbon atom 1 is glucosidic in character and removed with dilute acid. The second, the non-reducing end-group (B in Fig. 1) yields on hydrolysis 2,3,4,6-tetramethylglucose. The proportion of this non-reducing end-group gives a measure of the chain-length of starch. The method of determining the chain-length from the amount of tetramethylglucose obtained by hydrolyzing the fully methylated polysaccharide is referred to as the "end-group assay method."

Examination of the hydrolysis products of various methylated starches has shown that the proportion of tetramethylglucose liberated is always the same (between 4 and 5 per cent) and is independent of the biological source of the starch<sup>1</sup> (6, 7). A similar proportion of 2,3-dimethylglucose is also found among the hydrolysis products of methylated starch. The proportion of 4 to 5 per cent of tetramethylglucose corresponds to a terminated chain of 24 to 30 glucose units having a molecular weight of about 5,000. However, determination of molecular weights of various natural starches and their acetylated and methylated derivatives by physical methods such as by osmotic pressure, ultracentrifuge and viscosity

<sup>1</sup> End-group determinations have been made on starches from the following sources: potato, wheat, cassava, waxy maize, rice, horse-chestnut, banana and maize (Golden Bantam).

measurements show the starch molecule to have a much greater molecular weight than 5,000. Depending on the method of preparation of the acetylated and methylated derivatives, values ranging between 20,000 and 500,000 were obtained by different investigators for the molecular weight of starch (8, 9). The large discrepancy that exists between the molecular weights of starch as obtained by the end-group assay method and physical measurements is accounted for by the fact that the end-group assay method, showing a terminated chain of 24 to 30 glucose units and having a molecular weight of about 5,000, discloses not the total molecular size but the chain length of the branches in the much larger starch molecule.

Hydrolysis of methylated glycogen also produces 2,3,6-trimethylglucose and 2,3,4,6-tetramethylglucose (10). If, as in starch, the glycogen chains are finite in length, it is evident that each

lengths of 12 and 18 glucose units, having molecular weights of approximately 2,000 and 3,000, respectively. The molecular weight of glycogen determined by osmotic pressure measurements is in the region of 1,000,000 to 2,000,000 (9). There is evidence that undegraded glycogen has a molecular weight in excess of 4,000,000 (11), indicating that the glycogen molecule is made up of perhaps as many as 2,000 branches.

There is some difference in opinion in the details as to the manner in which the short chains or branches are combined to form the large starch or glycogen molecule. Haworth and Hirst (12, 13) consider that these branches (repeating units), each consisting of from 24 to 30 glucose residues in starch and 12 or 18 glucose residues in glycogen, are combined by "cross linkages" to form molecules of extremely large molecular weights. The chains are combined in such a way that the free

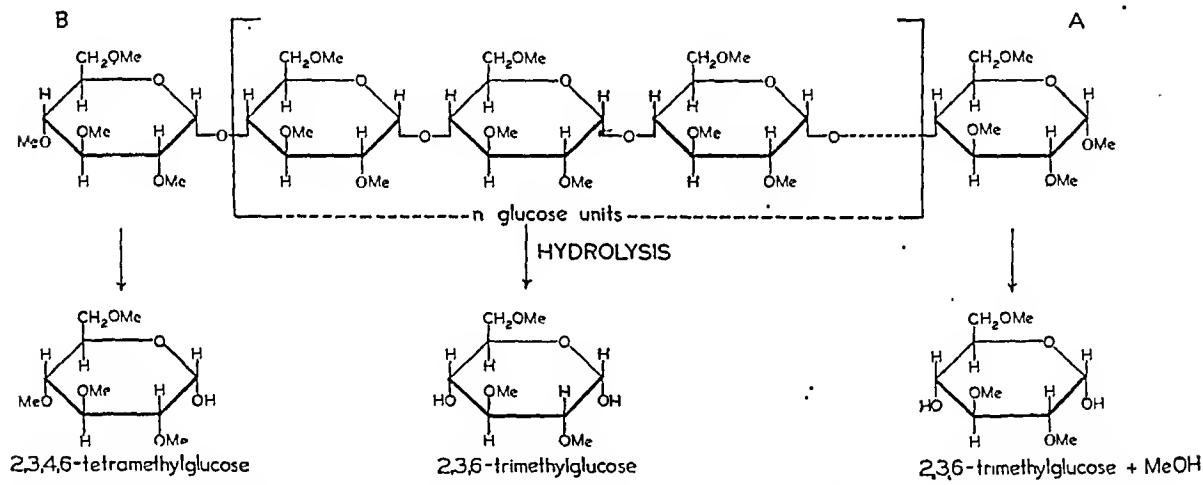


Fig. 1. Hydrolysis products of methylated starch or glycogen. (Starch,  $n = 22$  to 28; glycogen,  $n = 12$  or 18)

chain will possess a similar "reducing end-group" (A in Fig. 1) and a "non-reducing end-group" (B in Fig. 1). The proportion of tetramethylglucose (non-reducing end-group) obtained from methylated derivatives of glycogens from the liver or muscle tissues of a number of different animals is approximately 9 per cent.<sup>2</sup> An exception to this is the glycogen isolated from the liver of rabbits that have been fasted and then fed galactose or sucrose prior to the isolation of the polysaccharide (3). The methylated glycogen obtained from such animals, produces on hydrolysis 7 per cent of tetramethylglucose. The proportions of 9 per cent and 7 per cent "end-group" correspond to chain

reducing group of a glucose unit of one chain is glucosidically linked with the sixth hydroxyl group of a glucose unit in an adjacent chain, thus forming a "laminated" structure, shown in Fig. 2. The assumption of such "cross linkages" explains the presence of occasional glucose units with only two exposed hydroxyl groups, and accounts for the 2,3-dimethylglucose in methylated starch or methylated glycogen. It has been demonstrated that regardless of the method of preparation of starch methyl derivatives, whether the starch is methylated by a drastic or mild procedure, and irrespective of the molecular weight of the methylated starch, the percentage of end-group (tetramethylglucose) obtained on hydrolysis remains unchanged (8). The observed proportion of tetramethylglucose, therefore, cannot be attributed to random hydrolysis of long unbranched chains of similarly united residues during the

<sup>2</sup> Glycogens have been examined by the end-group method from the following animal sources: rabbit, horse, *Mytilus edulis*, dog, snail, dogfish, haddock, and hake, (Cf. ref. 7).

preparation of the methyl derivatives from starch. If this were the case, the proportion of end-group should vary depending on the method of preparation of the methylated starch and should increase as the molecular weight of the methylated starch decreases. This, however, is not the case. The link binding the branches in starch is considered a normal covalent bond (primary valence), intermediate in strength, between that of a furanose linkage, as in sucrose, and a pyranose linkage, as in maltose (13). Similarly, it is believed that the repeating units in glycogen are held by primary valences (14). Since it is now established that most starches are mixtures of two components, the unbranched amylose and the branched amylopectin, this conception of starch structure obviously applies to the amylopectin component.

Meyer and Fuld (15) take the view that branching in glycogen and amylopectin is multiple rather than single, as held by Haworth and Hirst (10). This view is based on methylation data as well as on the conclusion drawn from the manner in which

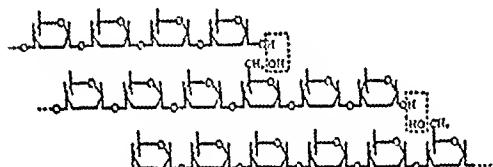


Fig. 2. Haworth and Hirst's diagrammatic formula for starch or glycogen. Each chain (repeating unit) contains 24 to 30 glucose residues in the case of starch, and 12 or 18 in the case of glycogen. [Cf. ref. 10, 13]

glycogen and amylopectin are degraded by certain enzymes. Methylated glycogen, assayed by the end-group method, contains one terminal glucose unit per eleven glucose residues (9 per cent tetramethylglucose). When glycogen is subjected to hydrolysis by  $\beta$ -amylase, 47 per cent is degraded to maltose. On methylation and hydrolysis of the 53 per cent of residual dextrin which has resisted the  $\beta$ -amylase, 18 per cent tetramethylglucose is produced, which is equivalent to one terminal group per every 5.5 glucose units. This indicates that the outer branches of the glycogen molecule, which are attacked by the enzyme, consist of six of seven glucose residues in  $\alpha$ -1,4-glucosidic union; 5.5 of these residues are split off by  $\beta$ -amylase, whereas one or two remain at the branching point, furnishing the terminal groups of the residual dextrin. Only short chains of an average of three glucose residues with free 2,3,6-OH groups are situated between these glucose residues whose 6-position is occupied by a branch. This conception of a ramified glycogen structure is represented in Fig. 3.

A similar view regarding the structure of amylopectin which involves the idea of multiple branching is held by Meyer and Bernfeld (16). The methylation end-group assay method shows that the amylopectin branches are from 25 to 28 glucose units in length. These branches are supposedly degraded with  $\beta$ -amylase to maltose, leaving a residual-dextrin I, to the extent of 55 per cent. At this stage of degradation, the branch points apparently offer an obstruction to further attack by this enzyme. The inference, therefore, is that the outside branches of amylopectin consist of 15 to 18 glucose units, whereas the inside parts of the chains, between branch positions, consist of 8 or 9 units. After the action of  $\beta$ -amylase on starch ceases, residual-dextrin I is attacked by  $\alpha$ -glucosidase (yeast maltase), but not with  $\beta$ -glucosidase (emulsin), with the production of glucose. The remaining substance (residual-dextrin II) can be attacked again by  $\beta$ -amylase yielding maltose and a residual-dextrin III. Since both the outside and inside branches in glycogen are shorter than in

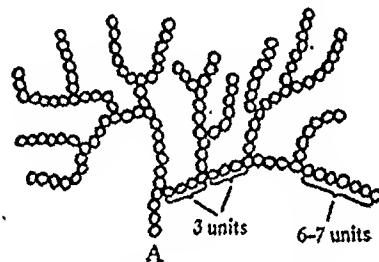


Fig. 3. Meyer's schematic representation of the branched glycogen molecule. [Cf. ref. 15]

amylopectin, glycogen leads itself to the building of a more compact molecule, which is almost spherical in shape (11).

Amylopectin, the branched component of starch, or its acetylated and methylated derivative can be resolved by fractional extraction with various solvents into fractions having different viscosities, and, therefore, presumably having different molecular weights. Amylopectin of maize starch is thus found to be a mixture of polymers having molecular weights from 50,000 to 1,000,000 (17, 18). Animal glycogen can also be separated into fractions possessing different viscosities. It may, therefore, be assumed that glycogen is probably also a mixture of branched polymers of various molecular weights (19).

There is some evidence indicating that the  $\alpha$ -linked glucose units in starch do not exist as extended linear chains, but as winding spirals. A screwlike model for starch was first suggested by Hanes (20) as a possible explanation for the formation of short chain dextrans in the breakdown of

starch by  $\alpha$ -amylase (Fig. 4). Freudenberg, *et al.*, (21) assume the existence of such a model in starch to explain the formation of closed ring Schardinger dextrans. When starch solutions are exposed to the action of the microorganism *Bacillus maccrans* a mixture of water soluble dextrans is produced from which two distinct, non-reducing crystalline compounds may be isolated,  $\alpha$  and  $\beta$  dextrans. These dextrans were first discovered by Schardinger about half a century ago and are known by his name. The Schardinger dextrans are completely non-reducing and upon methylation and subsequent hydrolysis produce 2,3,6-trimethylglucose as the sole product (22); this proves that they are closed ring structures. Inasmuch as there is now abundant evidence that the starch molecule consists of open branched chain structures, the existence of such closed rings in the starch molecule is not in accord with the present views on the con-

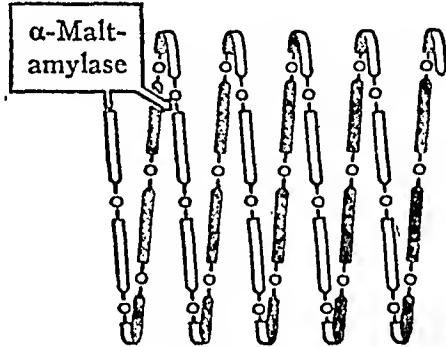


Fig. 4. Hanes' hypothetical starch model, showing the possible manner in which it is attacked by  $\alpha$ -amylase. [Cf. ref. 20]

stitution of starch. However, since it is known that some microorganisms are capable of synthesizing complex carbohydrates, there is good reason to believe that the Schardinger dextrans are not pre-formed in starch, but are formed in the process of enzymatic hydrolysis. Freudenberg postulates that *Bacillus maccrans* splits the starch chains to fragments containing 5 or 6 glucose residues and, because of the screwlike arrangement of the original spirals, every first and fifth or sixth glucose unit of these fragments are situated close to one another, and are able to unite and form rings of 5 or 6 glucose units.

To show that such a screwlike structure is possible from the standpoint of space configuration, Freudenberg constructed a model of  $\alpha$ -dextrin indicating the position of its atoms in space. The glucose units are situated perpendicular to the plane of the ring-shaped pentaglucosan (Fig. 5). The figure is based upon a *cis* form and the carbon atoms 1 and 4 lie in one plane of the equilateral pentagon. The C—O bond connecting the glucose units lie in a straight line. Because of the particu-

lar angle of the oxygen an equilateral pentagon is formed with five oxygen atoms of the 1,4 linkages situated in one plane. In  $\beta$ -dextrin, with six glucose units, the corner oxygen atoms lie in two planes. However, recent X-ray data presented by French and Rundle (23) show that the  $\alpha$ -dextrin (cyclohexaamylose) contains six glucose residues, while the  $\beta$ -dextrin (cycloheptaamylose) contains seven glucose residues in the ring.

The assumption that *Bacillus maccrans* splits off starch fragments of 6 or 7 glucose units and then unites them through the terminal glucose residues into rings is perhaps the simplest hypothesis for the mechanism of formation of the Schardinger dextrans. However, there is no experimental evidence for this mechanism. The assumption of

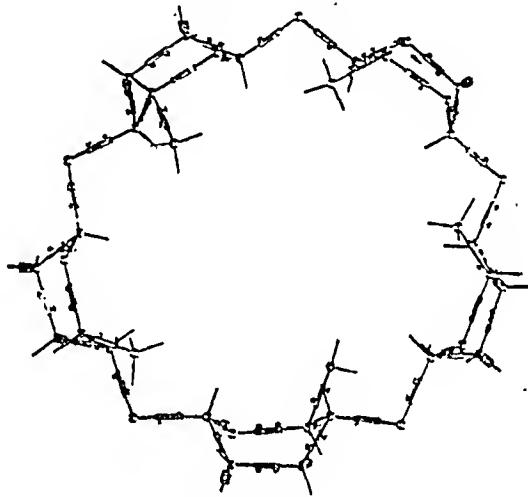


Fig. 5. Freudenberg's model for  $\alpha$ -dextrin (Schardinger's dextrin), illustrating the relative space positions of the atoms of the glucose units. [Cf. ref. 21]

other mechanisms, such as splitting off of successive anhydroglucosidic units from the starch chains, which are then used for the synthesis of closed ring dextrans, cannot be at present excluded.

It is generally agreed that in solution the starch macromolecule is held together only by primary valences. However, there is evidence indicating that the macromolecules themselves are associated by hydrogen bonds to form large particles. It has been observed that starch always exists in plants in granular form just as cellulose appears in the form of fibers, or some proteins as globules. The assumption is that the hydrogen bond is probably the intermolecular force which determines the mode of occurrence and is responsible for the specific properties of these natural materials. The granule is disrupted by hot water and acids, agents known to affect hydrogen bond formation. The starch granule may also be directly methylated to give a product with a molecular weight of about

half a million. When methylated, the starch derivative does not reprecipitate in the granular form, however (13). This is apparently due to the substitution of the hydroxyl groups by methoxyl groups, which do not form hydrogen bonds.

#### The amylose and amylopectin components of starch

The names, amylose and amylopectin, used earlier in a different sense, are still retained by most investigators to describe the two starch components. The chief chemical difference that distinguishes amylose from amylopectin lies in the fact that the former is constituted of unbranched chains of glucose residues, joined only through  $\alpha$ -glucosidic-1,4-linkages, while the latter also contains  $\alpha$ -glucosidic-1,6-linkages, which are present at the branching points. The two starch components can be separated by a number of different procedures, such as hot water extraction, electrodialysis, and butanol precipitation.

When starch is swollen in water at a temperature of approximately 70°C., the grains are not ruptured and the crude amylose can be extracted from the swollen grains and separated by settling or centrifuging. Since the amylose can be leached out from starch granules with hot water, it appears that its solubility in the starch granule is greater than that of amylopectin. However, the amylose becomes more insoluble than the latter after it has been precipitated and dried. The small amount that dissolves rapidly retrogrades from solution. The more completely the amylose is separated from the amylopectin, the more insoluble the amylose becomes. The retrogradation of the amylose is attributed to its greater orderliness of molecular orientation and tendency to exist in the crystalline state.

Schoelch (24) introduced a unique method for separating amylose from starch by using butanol as a selective precipitant. When a dilute starch solution saturated with butyl alcohol is autoclaved and cooled, the amylose precipitates in the form of six-leaved rosettes or microscopic needles which can be separated by centrifuging. Applying the butanol precipitation method to a hot water extract, Kerr and Severson (25) obtained what appeared to be single crystals of amylose (Fig. 6).

Complete methylation of amylose and separation of the methylated sugars after hydrolysis produces approximately 0.3 per cent of tetra-methylglucose, an amount of "end-group" corresponding to an approximate chain length of 300 glucose units (26, 27). This value is of the same order of magnitude as the molecular weight determined by viscosity and osmotic pressure measurements, indicating that amylose consists of a single long unbranched chain of about 300 glucose units. The fact that no significant amount of dimethyl-

glucose can be detected from the hydrolysis products of methylated amylose supports this conclusion. This does not, however, exclude the possibility that the value of 300 represents an average of longer and shorter chains of amylose. When amylopectin and unfractionated starch are subjected to the action of  $\beta$ -amylase, the enzymatic hydrolysis ceases when approximately 55 per cent and 60 per cent of these materials, respectively, are converted into maltose. The difference in behavior of  $\beta$ -amylase toward amylose and amylopectin is in accord with the view that the former is an unbranched while the latter is a branched molecule. It is assumed that  $\beta$ -amylase attacks the non-reducing ends in the starch molecule, splitting off successive maltose fragments. Since branching in amylopectin occurs on the 6th carbon of some of the glucose units in the chains, these 1,6-linkages are probably responsible for



Fig. 6. (a) (Left) Schoelch's amylose (butanol precipitated fraction of potato starch, stained with iodine.  $\times 150$ ) (b) (Right) Kerr's crystalline corn amylose. ( $\times 200$ ) [Cf. ref. 24, 25]

stopping the hydrolysis at or near the points of branching. With amylose, having an unbranched structure and, therefore, no such linkages, the hydrolysis by  $\beta$ -amylase continues until the whole molecule is degraded to maltose.

Amylose, existing in the potato starch to the extent of about 20 per cent, produces a blue color when treated with iodine which is approximately six times as intense as that of amylopectin, and three times as intense as the color given by unfractionated starch (28). The production of the blue color when starch is treated with iodine is, therefore, chiefly a property of the amylose fraction. The property of amylose to bind iodine preferentially when in admixture with amylopectin has been made the basis of a quantitative method for the determination of amylose in starches. Thus Bates, French, and Rundle (29) demonstrated the amylose content of the various starches to be as follows: tapioca 17, rice 17, banana 20.5, corn 21, potato 22, popcorn 23, wheat 24, sago 27, and lily

bulb 34 per cent. Waxy rice, waxy sorghum, waxy corn, and waxy barley starches are entirely devoid of amylose.

### Synthetic starches

The isolation of glucose-1-phosphate (Cori ester) and of the enzyme muscle phosphorylase, paved the way for the synthesis of polysaccharides having glucose, linked through  $\alpha$ -1,4-glucosidic linkages, as the fundamental unit. Cori and Cori (30) succeeded in synthesizing *in vitro* a polysaccharide by the action of the enzyme, phosphorylase, from muscle extract on glucose-1-phosphate. A similar polysaccharide was synthesized by Hanes (31) from the same ester with the aid of an enzyme from the potato tuber. It is interesting to note that both of these polysaccharides are closely related to the amylose fraction of starch. Like amylose, the synthetic polysaccharides are slightly soluble in water, rapidly retrograde from solution on standing, and produce a sharp X-ray V-diffraction pattern. They give a very intense blue color with iodine and are completely converted to maltose by  $\beta$ -amylase. Data obtained by the end-group method show that like amylose the synthetic starches are made up of unbranched chains of glucopyranose units. The polysaccharide synthesized by the action of potato phosphorylase has an average chain length of 100 glucose units (32, 33); the polysaccharide produced by the action of muscle phosphorylase is approximately 200 units in length (34). However, not all the known synthetic polysaccharides possess an unbranched chain structure. The polysaccharide synthesized *in vitro* by heart or liver phosphorylase (35) exhibits the properties of natural glycogen. It is soluble in water, gives a reddish-brown color with iodine, does not retrograde from solution, and produces a diffuse X-ray pattern characteristic of amorphous material. These properties indicate a branched chain structure. Haworth, *et al.* (36), have also recently reported the preparation of an enzyme solution from potato which converts glucose-1-phosphate into a polysaccharide, probably identical with the amylopectin component of natural starch. It is soluble in water and produces a purple-red color with iodine. When acted upon by  $\beta$ -amylase, the hydrolysis is arrested, as in the case of natural amylopectin, before conversion into maltose is completed. The end-group assay method shows that the chains in this polysaccharide consist of about 20 glucose units.

### Starch-iodine color reaction

Freudenberg (21) explains the blue starch-iodine color by assuming that starch possesses a helical structure. When treated with iodine, the iodine molecules enter the starch spirals and are deposited in the center of the helices. The hydrogen

of the first and fourth carbon atoms of each glucose unit form a hydrocarbon lining within the spiral, measuring about 5 Å across the unfilled open space. An iodine molecule, 6.3 Å long and 3.8 Å thick, can fit vertically within this spiral so that there is one molecule of iodine for each sequence of 10 CH groups. In a hydrocarbon medium iodine is known to give a blue color, rather than the red color produced in water or other polar solvents. In short chain dextrans of about six glucose units produced from starch by degradation with amylose or treatment with acid, this arrangement of CH groups in the fragments is destroyed and, therefore, produces no color when treated with iodine. Meyer and Bernfeld (37) do not consider this an adequate explanation, claiming that some substances known not to have a helical structure, such as methylated cellulose, or cellulose which has been swollen with zinc chloride, also give a blue color with iodine. According to these authors, the explanation of the blue iodine color resides in the colloidal structure of these compounds.

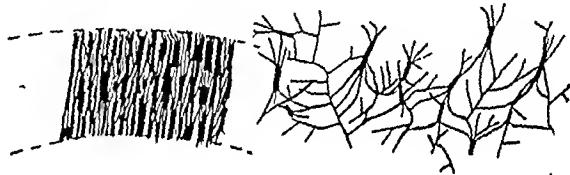


Fig. 7. (a) (Left) Crystalline micelles (thick lines) in layer of a starch grain. (b) (Right) Open network structure of swollen amylopectin. The connected crystalline micelles are shown by thick lines. [Cf. ref. 41]

Rundle and collaborators (38, 39) point out that, since no one model is capable of explaining the many known colored iodine compounds other than starch, Meyer's criticism of the helical starch model is not serious. Rundle, *et al.*, present further evidence to strengthen Freudenberg's view by showing that starch-iodine solutions exhibit dichroism of flow, the light with its electric vector parallel to the flow lines is more strongly absorbed than light with its electric vector normal to the flow lines. The dichroism of flow requires that the long axes of the iodine molecules in the complex be parallel to the long axis of the starch-iodine complex. They believe that the optical properties of starch-iodine complexes may be best interpreted in terms of helical starch chains.

### Crystalline nature of starch

Starch placed in the path of an X-ray beam produces diffraction patterns characteristic of crystalline material, showing the existence of a molecular orientation (40). The term "crystalline," as applied to starch, should not be interpreted in the same sense as when referred to compounds having

individual visible crystals. According to Meyer (4), certain regions of the starch granule contain submicroscopic areas where portions of several chain molecules are oriented together by secondary valences, probably hydrogen bonds. These regions, forming lattice-like arrangements and constituting part of the structure of native starch, are termed "crystallites" (Fig. 7). They are destroyed when starch is gelatinized in hot water, but are reformed when the gel is allowed to retrograde. In the case of unbranched long-chained amylose molecules or with shorter branches of amylopectin, the chains are partially oriented, resulting in the formation of such crystalline regions. In the areas between the crystalline regions, such orientation is lacking and these non oriented molecules make up the amorphous material of the starch granule. Glycogen, consisting entirely of multi-branched short molecules, cannot form a regular arrangement with other molecules, which accounts for the fact that this polysaccharide always exists in amorphous state and produces a diffuse X-ray pattern.

#### *Non-carbohydrate substances in starch and glycogen*

For a long time the concept prevailed that starch exists in organic combination with non-carbohydrate materials such as phosphorus, fatty acids, and silicic acid. It has recently been shown that, except for phosphorus, these materials exist in starch as impurities which can be eliminated by careful purification.

Schoch (42) has demonstrated that the fatty acid material in corn, rice, and wheat starches can be removed without hydrolytic degradation by extraction with water-miscible fat solvents such as methanol or 80 per cent dioxane. Similarly, Lehman (43) arrived at the conclusion that the fatty acids associated with starch are probably adsorbed. While the greatest proportion of the phosphorus material can be extracted with hydrophilic fat solvents from corn, wheat, and rice as lipid material, the same treatment removes only a very small fraction of the phosphorus in potato starch (42). This phosphorus, which constitutes about 0.09 per cent of the starch, is probably esterified with the carbohydrate, but it is doubtful whether this small amount plays any significant role in the metabolism of this polysaccharide. Ling and Nanji's (44) claim that starch is linked with silicic acid in form of an ester is not substantiated by recent work.

Similarly, the belief that glycogen exists in organic combination with phosphorus (45) has now been discarded. Somogyi (46) has shown that glycogen prepared by precipitation with dilute alcohol (33 per cent) is practically free of phosphorus and nitrogen.

The author is grateful to Dr. R. W. Kerr and to Dr. T. J. Schoch of the Corn Products Refining Company for their photomicrographs of the crystalline amyloses.

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## THE MECHANISM OF FORMATION OF STARCH AND GLYCOGEN

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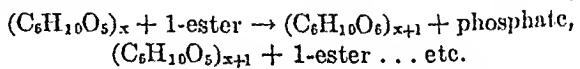
When one considers the reaction, (n) glucose-1-phosphate  $\rightarrow$  (n)PO<sub>4</sub> + polysaccharide, one might believe that 2 or more glucose-1-phosphate molecules can react with the enzyme in such a manner that an  $\alpha$ -glucosidic chain is started which grows by further additions of glucose-1-phosphate units. Actually, no reaction takes place when highly purified materials (crystalline muscle phosphorylase or purified potato phosphorylase and synthetic glucose-1-phosphate) are used, even when enzyme and substrate are incubated for many hours. Glycogen or starch has to be added to the reaction mixture in order to obtain polysaccharide synthesis from glucose-1-phosphate (1, 2, 3).

The rate of the reaction, all other conditions being constant, depends on the nature as well as the amount of activating polysaccharide which is added. Of the two polysaccharides which make up natural starch, the branched portion (amylopectin) has activating power, while the linear portion (amylose) has little effect in concentrations in which amylopectin is strongly activating. On comparing amylopectin and glycogen, one finds that the former has more activating power for potato phosphorylase than the latter, while the reverse is true for muscle phosphorylase. These two enzymes can be used as tools for the differentiation of polysaccharides in a manner which will be described later.

*Kinetics of polysaccharide activation.* The effect of glycogen concentration on the rate of reaction of glucose-1-phosphate (1-ester) is shown in Fig. 1. When no glycogen is added, no reaction occurs; with 10 mg. percent some 1-ester is converted to

polysaccharide, but the reaction fails to reach equilibrium even in 20 hours; with 40 mg. per cent the reaction reaches equilibrium at a rate which falls off more rapidly than that of a first order reaction; with 500 mg. per cent the reaction proceeds at maximum rate and is kinetically of the first order throughout its course.

The following explanation has been offered for this kinetic behavior (4). The activating polysaccharide is one of the participants in a bimolecular reaction, as formulated in the introduction to this symposium, and its concentration would therefore be expected to influence the rate. In an abbreviated form the reaction may be written as follows:



According to this hypothesis polysaccharide synthesis consists in a lengthening of the side chains or branches of the activating polysaccharide by a repetition of the process formulated above until chain length becomes a factor limiting the rate. This would explain why polysaccharides with many branches and short chain length, amylopectin (4.5 per cent end groups) and glycogen (9 per cent end groups) have strong activating power, while the linear polymer, amylose (0.3 per cent end groups) has little effect. It would also explain why the linear polysaccharide formed by phosphorylase itself has no activating effect during the course of the reaction.

In the following calculations, the assumption has been made that all the branches indicated by end group determinations are used as nuclei for

polysaccharide synthesis. Accordingly, a glycogen solution of 0.02 per cent (at which concentration the initial rate of the reaction is half maximal) would contain  $1.1 \times 10^{-4}$  M terminal glucose units. The chain length of the newly formed polysaccharide would then depend on the concentration of the added glucose-1-phosphate; if it were  $1.8 \times 10^{-2}$  M, as in the experiments in Fig. 1, the average chain length attained at equilibrium, corresponding to a conversion of 78 per cent of the added 1-ester, would be about 130 glucose units.

A similar calculation for the experiment with 0.5 per cent glycogen would give an average chain length of only 5 glucose units. Many short polysaccharide chains would be formed, so that chain length would not become a factor limiting the rate of the reaction. Furthermore, the reaction, although bimolecular, would be kinetically of the first order, because the concentration of one of the

experiments have shown that when enough glycogen is added at this point to raise its concentration to 0.5 per cent, full enzyme activity is restored immediately (1).

The time required for the reaction to reach equilibrium in the presence of low concentrations of activating glycogen depends on the enzyme concentration (4). It has been found that the maximal chain length which can be built up when high concentrations of muscle phosphorylase are used is about 200 glucose units and that, if the initial ratio of concentrations, glucose-1-phosphate/terminal glucose units of glycogen, is greater than 200, the reaction fails to reach equilibrium. This is illustrated in table I.

TABLE I

*Chain length of polysaccharide synthesized by muscle phosphorylase*

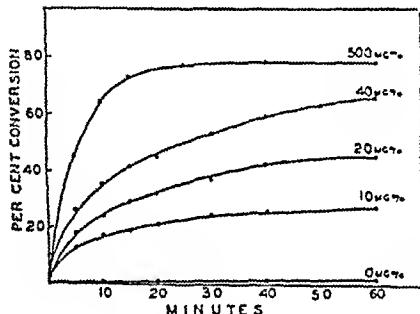


Fig. 1. Effect of glycogen concentration on the rate of conversion of glucose-1-phosphate to polysaccharide by crystalline muscle phosphorylase.

two reactants, the terminal glucose units, would remain constant. It may also be seen why the equilibrium, within certain limits, is independent of the concentration of the added glycogen, a fact which has been established experimentally for concentrations ranging from 0.02 to 1 per cent (1). If the usual mass law expression is written,

$$K = \frac{\text{terminal maltosidic linkage}}{\left[ \begin{array}{c} \text{terminal} \\ \text{glucose} \end{array} \right] \left[ \begin{array}{c} \text{phosphate} \\ \text{glucose-1-phosphate} \end{array} \right]}$$

two of the concentration terms cancel each other, and the value of the equilibrium constant, at a given pH, will be solely determined by the ratio, phosphate/glucose-1-phosphate.

The experiment with 0.01 per cent of activating glycogen in Fig. 1 shows that only 25 per cent of the added 1-ester had been used up at a time at which the reaction had become very slow. Other

GLYCOGEN ADDED mg. %	terminal glucose units $M \times 10^{-4}$	ADDED 1-ESTER WHICH REACTION		CHAIN LENGTH cal. calc.
		%	$M \times 10^{-2}$	
45	2.5	40	3.8	152
41	2.3	45	3.6	157
49	2.7	51	5.9	218
50	2.8	61	6.5	232
54	3.0	61	0.9	230
56	3.1	65	7.2	232
60	3.3	74	7.4	224
40	2.2	77	4.8	223
90	5.1	78	8.3	163
54	3.0	62	6.1	203

*End group determination on pooled sample:*

Total tetramethylglucose .....	0.95%	105
Correction for added glycogen .....	0.40%	
Tetramethylglucose in synthetic polysaccharide. 0.55%		180

The data in this table, which have not been presented before, were taken from individual experiments in which a large amount of synthetic polysaccharide was prepared for end group determinations (5).

The average amount of glucose-1-phosphate which had reacted at the end of 18-20 hours was 62 per cent of the amount added. Had equilibrium been reached, 80 per cent should have reacted. It may be seen that the reaction stopped when a chain length of 150 to 230 glucose units had been reached.

The polysaccharide obtained in the nine preparations was pooled and amounted to 15.2 gm. plus 0.76 gm. of glycogen which had been added to prime the reaction and which could not be separated from the synthetic polysaccharide. These figures alone would be sufficient to indicate chain

length, since  $15.2/0.076 = 200$ . End group assay by Dr. Hassid showed 0.95 per cent tetramethyl-glucose which corresponds to an average chain length of 105 glucose units. The discrepancy between this value and the calculated one may be due to the breaking off of the long chains, whereby an additional end group would be exposed for each chain which is broken off. On this assumption a correction has been applied for the added glycogen; the average chain length of the synthetic polysaccharide obtained from end group assay and by independent calculation then shows satisfactory agreement.

Experiments similar to those in table I were carried out with amylopectin and amylose as activating polysaccharides (6). The maximal chain length which could be built up by muscle phosphorylase with amylopectin as activator was somewhat less than with glycogen.

Amylose, which is poorly soluble in water, was dissolved in 3 N KOH and neutralized with HCl. In this manner sufficiently concentrated and stable solutions could be prepared for these tests. It was necessary to use amylose in a final concentration of 500 mg. per cent in order to get an appreciable phosphorylase activity. If it is assumed that the amylose has an average chain length of about 200 glucose units, this would correspond to  $1.4 \times 10^{-4}$  M end groups and would be equivalent in end groups to a glycogen concentration of 25 mg. per cent. The initial rate of the reaction with 500 mg. per cent amylose was about the same as with 25 mg. per cent of glycogen and was therefore proportional to the number of end groups offered, but the number of glucose units which could be added to amylose was very small. After 20 hours of incubation with 500 mg. per cent amylose 23 per cent of the added 1-ester or  $3.1 \times 10^{-3}$  M had reacted and this would correspond to a newly formed chain length of only 22 glucose units. The total chain length would therefore be about 220 glucose units and this is of the same order of magnitude as the maximal chain length which is built up with glycogen as the activating polysaccharide.

It should be emphasized that the results discussed so far apply only to muscle phosphorylase, an enzyme which can be prepared in a high state of purity. In experiments with potato phosphorylase it was found that chain length was not a factor limiting the rate. This was indicated by the observation that equilibrium could be reached when low concentrations of amylose were used as the activating polysaccharide. This experiment will have to be repeated when the enzyme as well as the amylose have been subjected to further purification. At the present stage of purity of the potato enzyme the presence of the branching factor which is described in the next section cannot be ex-

cluded.<sup>1</sup> Other enzymes which are present in crude preparations of potato phosphorylase and which could interfere are  $\alpha$ -amylase and phosphatase. The former splits amylose into fragments which activate potato phosphorylase, while the latter splits the 1-ester and thus simulates phosphorylase activity.

*Structure of synthetic polysaccharides.* It was surprising to find, when muscle phosphorylase was first prepared (7), that the polysaccharide formed by it gave a blue color with iodine, while preparations of brain, heart, liver and yeast phosphorylase formed a polysaccharide which gave a brown or purplish-brown color with iodine. Subsequent work with synthetic polysaccharides prepared with potato or muscle phosphorylase showed the great similarity of these products to the amylose fraction of natural starch with respect to solubility characteristics, x-ray diffraction patterns,

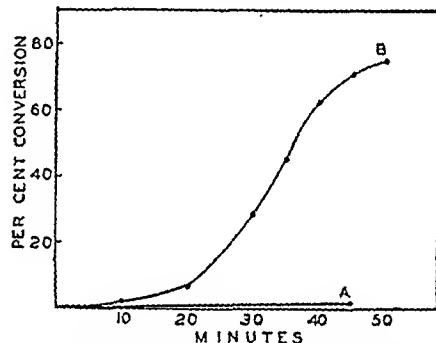


Fig. 2. Activity of muscle phosphorylase when combined with supplementary enzyme from liver. No glycogen was added to prime the reaction. Curve A, muscle phosphorylase or supplementary enzyme alone. Curve B, the two enzymes combined.

intensity of coloration with iodine, digestibility by  $\beta$ -amylase, number of end groups, and low activating power for phosphorylase (5, 8).

The polysaccharide formed by liver phosphorylase resembled glycogen in solubility, the amorphous nature of its x-ray diffraction pattern, coloration with iodine, and activating power for phosphorylase. It seemed likely that the relatively impure enzyme preparations of liver and heart contained an additional factor which, in combination with phosphorylase, resulted in the formation of a branched type of polysaccharide. Water extracts of skeletal muscle for an as yet unknown reason yield only traces of this factor.

<sup>1</sup> The potato phosphorylase was prepared by Dr. A. A. Green and had 10-15 units per mg. protein. One unit corresponds to the formation of 0.1 mg. P in 5 minutes under standard conditions; starch 500 mg.%, glucose-1-phosphate, dipotassium salt, 750 mg.%, M/10 citrate buffer pH 6.5, temp. 30°.

That the factor is enzymatic is indicated by the observation that when crystalline muscle phosphorylase is combined with a heat-labile protein fraction of liver or heart, a polysaccharide is formed which gives a brown color with iodine and which activates phosphorylase (9). A striking type of activity curve is obtained when no glycogen is added (except for the traces that are introduced with the liver or heart protein fractions). This is illustrated in Fig. 2. Neither phosphorylase alone nor the supplementary enzyme alone show any measurable activity; when both are combined one finds a pronounced induction period, followed by an autocatalytic curve. An autocatalytic curve would result if a polysaccharide were formed which had an activating power similar to that of glycogen. That this was the case was shown by the isolation of the polysaccharide by treatment with strong alkali and precipitation with alcohol. In a concentration of 30 mg. per cent it had as much activating power for phosphorylase as an equal concentration of glycogen prepared from liver by Pflueger's method (9).

The formation of a branched type of polysaccharide appears to be due to the simultaneous action of two enzymes, one being phosphorylase which is specific for  $\alpha$ -1,4-glucosidic linkages and the other an enzyme which makes 1,6-glucosidic linkages and thus starts branches which can grow in length through the action of phosphorylase. Depending on the ratio of the two enzymes, a variety of branched type of polysaccharides could be formed such as glycogen, amylopectin, corn glycogen and others, each differing somewhat in structure. Evidence for differences in structure of these polysaccharides is presented in the next section.

In a preliminary note Haworth, Peat and Bourne (10) have reported the occurrence of a branching factor in extracts of potatoes which (presumably in combination with phosphorylase) forms a polysaccharide that resembles amylopectin in a number of properties.

*The differentiation of polysaccharides by means of muscle and potato phosphorylase.*<sup>2</sup> A comparison of the activating power of different polysaccharides for the two enzymes is shown in table II. The polysaccharides were dissolved in water, with heating if necessary, and filtered; their concentration was determined by means of glucose estimations after acid hydrolysis. They were then adjusted to equal concentrations for enzyme tests. The range of concentrations tested was between 20 and 60 mg. per cent in the different experiments.

It has been found that the combination of starch and amylopectin with the potato enzyme and of glycogen with the muscle enzyme (4) is expressed by the equation,  $v = \frac{V \times c}{k + c}$ , where  $c$  is the concentration of the activating polysaccharide,  $V$  the maximal enzyme activity attained at high concentrations of  $c$ , and  $v$  the enzymatic rate observed at a given concentration of  $c$ . The constant,  $k$ , gives a numerical value for the concentration at which one half of the enzyme is combined with the activating polysaccharide and corresponded to 12-15 mg. per cent for starch and amylopectin and 20 mg. per cent for glycogen in the experiments with the two enzymes referred to above.  $k$  was not determined for the other polysaccharides; they were merely compared with respect to  $v$  when  $c$  was kept constant.

Schoch's amylose showed an anomalous behavior in tests with the potato enzyme. The value of  $k$  decreased progressively as the concentration of amylose was increased. This may be due to the presence of impurities with an activating power greater than that of amylose. Such a possibility is also suggested by the observation of Green and Stumpf (3) and of Hidy and Day (11) that amylose synthesized by potato phosphorylase *in vitro* has practically no activating effect on the enzyme.

Further differentiation was obtained when these polysaccharides were hydrolyzed in acid for various lengths of time and the split products, after neutralization, were tested for their activating power. The per cent hydrolysis was determined by means of a copper reagent of high alkalinity and heating for 30 minutes. The hydrolysis of amylose, amylopectin and maltose in 7.7 N HCl at 30° followed first order kinetics throughout its course and gave a velocity constant of  $1.05 \times 10^{-3} \text{ min.}^{-1}$ . The hydrolysis of glycogen was less regular and the constant was about 10 per cent lower. It is to be noted that 6 N HCl was used in the experiments with the muscle enzyme and that the rate of hydrolysis of polysaccharides in 6 N HCl was only one fourth that found in 7.7 N HCl.

Characteristic curves were obtained when enzyme activity was plotted against time or per cent of hydrolysis of the polysaccharides. Only the salient features of these curves are given in table II.

Liver glycogen is characterized by an immediate rise in its activating power which occurs before an appreciable hydrolysis has taken place and which is more marked with the potato than with the muscle enzyme. The activity of the latter enzyme declines sharply on continued hydrolysis of glycogen and it is for this reason that a lower acid concentration was chosen, otherwise the initial rise in activity can easily be overlooked. After treatment with 7.7 N HCl for 120 minutes the activating

<sup>2</sup> The observations recorded in this and in the following sections, except where indicated, are from unpublished experiments. This work was supported by a grant from the Corn Industries Research Foundation.

effect of glycogen for muscle phosphorylase has practically disappeared, while the activity for potato phosphorylase shows little decline, even after longer periods of hydrolysis. A sample of liver glycogen which was non-opalescent in 10 per cent solution was prepared by Dr. Somogyi by treatment with weak acid. The effect of this treatment is noticeable in the enzyme tests, since this material has more activating power for both enzymes than glycogen not exposed to acid.

tato phosphorylase. Applying these criteria, it may be seen that the so-called glycogen of sweet corn described by Morris and Morris (13) resembles amylopectin rather than glycogen. Since this polysaccharide is kept in solution in 66 per cent acetic acid in the method of its separation from starch, it is probably somewhat degraded.

Hidy and Day (11) subjected amylose to hydrolysis in about 7.5 N acid at 27 to 28° and found that its ability to activate potato phosphorylase

TABLE II

*Activating effect of various polysaccharides (in concentrations of 20 to 60 mg. per cent) on muscle and potato phosphorylase*

Polysaccharides dissolved in water or hydrolyzed in HCl at 30° for various periods.

Comparisons were made with equal concentrations of polysaccharides and of enzyme and are expressed in per cent of standard, glycogen in water for muscle and amylopectin in water for potato enzyme.

POLYSACCHARIDE	METHOD OF PREPARATION*	SOURCE	MUSCLE ENZYME				POTATO ENZYME			
			Poly-sacch. in H <sub>2</sub> O Activity	Polysacch. in 6 N HCl Activity	Time	Hy-drolysis	Poly-sacch. in H <sub>2</sub> O Activity	Polysacch. in 7.7 N HCl Activity	Time	Hy-drolysis
glycogen .....	with or without heating in KOH	liver	100	140 34	25 140	2 8	20	80	10-120	2-22
glycogen, non-opalescent.	Somogyi *	liver	109				61			
"glycogen".....	Chargaff	tubercle bacilli	33	110 36	25 140	2 8	12	50	10-60	2-14
"glycogen".....	Hassid	sweet corn	70	56 23	30 200	2 12	86	83	10-60	2-14
starch.....	U.S.P.	corn	45				82			
soluble starch.....			45				82			
amylopectin .....	Schoch	corn	64	46 12	30 200	2 12	100	88	10-120	2-25
amylose.....	Schoch	corn	10	5	100		32			see Fig. 3
amylose .....	synthetic	potato or muscle phosphoryl.	0				3			
β-Schardinger dextrin...	Hudson	b. macerans acting on starch	0	0			0			see Fig. 4

\* The supply of the materials by the authors listed is gratefully acknowledged.

The bacterial glycogen of Chargaff and Moore (12) is of particular interest since it is rather homogeneous and has a particle weight of 12 million as calculated from rates of sedimentation and diffusion. Short treatment of this macro-molecule with acid markedly increases its activating power for both enzymes.

Amylopectin behaves quite differently from glycogen when the first stages of acid hydrolysis are compared. An increase in activating power cannot be demonstrated either with muscle or po-

increased up to the aehromic point and then decreased. This observation has been confirmed and extended. The same authors reported a marked increase in the activating power of starch, when subjected to acid hydrolysis. In our experiments a relatively slight increase was noted which was the same as that obtained with a mixture of 80 per cent amylopectin and 20 per cent amylose, the proportion in which these polysaccharides occur in corn starch. Since amylopectin alone did not show an

increase in activating power on acid hydrolysis, that of starch is due to its amylose content.

A curve showing the relation between enzyme activity and per cent hydrolysis of amylose is shown in Fig. 3. Initial parts of curves for amylopectin and glycogen are included for comparison. It may be seen that enzymic activity reached a peak when 30 per cent of the amylose had been hydrolyzed. The average chain length at this point was determined in the following manner. The hydrolysis products of amylose were subjected to yeast fermentation which removed glucose and maltose, neither of which activates phosphorylase. The reducing power of the unfermented dextrins showed a five fold increase after complete hydrolysis in acid; hence the average chain length of the dextrins was about 5 glucose units when the enzyme activity in Fig. 3 reached its maximum.

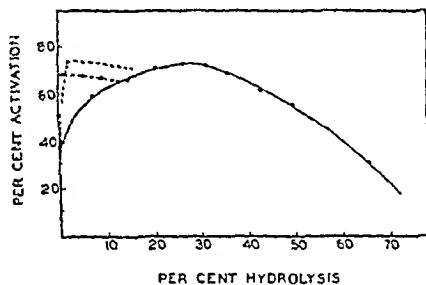


FIG. 3. Effect of products of acid hydrolysis of amylose on activity of potato phosphorylase. Solid line, amylose; dashed line, glycogen; open circle, amylopectin, all tested in a concentration of 32 mg. per cent. Enzyme activity expressed in per cent of maximum activity with 500 mg. per cent starch.

This finding would indicate that potato phosphorylase can be activated by relatively short polysaccharide chains. A direct confirmation is seen in the fact that the cyclic  $\beta$ -Schardinger dextrin which contains only 7 glucose units can be converted by acid hydrolysis into open-chain dextrins which activate potato phosphorylase. The same result has been obtained with the  $\alpha$ -Schardinger dextrin which contains 6 glucose units. The hydrolysis products of  $\alpha$ - or  $\beta$ -Schardinger dextrans or of amylose do not activate muscle phosphorylase, a clear indication that the requirements of this enzyme for activating polysaccharide are quite different.

When amylose is hydrolyzed with salivary diastase ( $\alpha$ -amylase), its activating power for the potato enzyme increases in a manner similar to that observed on acid hydrolysis of amylose. Hydrolysis of amylose with  $\beta$ -amylase results in a decrease in activating power for potato phosphorylase which is quite marked when hydrolysis

reaches 30 per cent. When the outer branches of amylopectin are removed by the action of  $\beta$ -amylase, the residual dextrin has very little activating power for potato phosphorylase.

*Hydrolysis of Schardinger dextrans.* The kinetics of acid hydrolysis of the  $\alpha$ -1,4-glucosidic linkages in the Schardinger dextrans are of some interest. One would expect that the rate constant in 7.7 N HCl at 30° would be the same as that found for the  $\alpha$ -1,4-glucosidic linkages in amylose, namely,  $1.05 \times 10^{-3}$  min.<sup>-1</sup>. Actually, the hydrolysis of Schardinger dextrans does not follow first order kinetics, when the increase in reducing power is taken as a measure. The rate constants are low at early stages of acid hydrolysis and increase steadily, reaching a final value of  $1 \times 10^{-3}$  min.<sup>-1</sup> only when more than 50 per cent has been hydrolyzed. In order to analyze this finding it was necessary to determine the amounts of unchanged Schardinger dextrans remaining at different times of acid hydrolysis. This was done by subjecting the hydrolysis products to the successive action of  $\beta$ -amylase and of yeast which procedure removes the open-chain dextrans. The unopened rings of the Schardinger dextrans which are not attacked by these enzymes can then be determined as glucose after acid hydrolysis.

It was found that the opening of the rings during acid hydrolysis follows first order kinetics and that the rate constant for the  $\beta$ -Schardinger dextrin is  $3.4 \times 10^{-3}$  min.<sup>-1</sup>, and that for the  $\alpha$ -dextrin somewhat lower. In either case the opening of the rings occurs faster than the subsequent hydrolysis of the open-chain dextrans and this suggests that one is dealing with a consecutive reaction of the type,  $A \xrightarrow{K_1} B \xrightarrow{K_2} C$ , where  $A$  represents the concentration of the Schardinger dextrans,  $K_1$  the rate constant for the opening of the rings,  $B$  the concentration of the open-chain reducing dextrans and  $K_2$  the rate constant for the hydrolysis of the  $\alpha$ -1,4-glucosidic linkages in  $B$ .  $C$  was determined as glucose and maltose by differential fermentation with yeast. By deducting  $C$  from  $A$ , the concentration of  $B$  could be calculated.

In Fig. 4 it is shown that the curve representing the concentration of the open-chain dextrans parallels the enzyme activity curve. The shape of the latter curve (as that of the corresponding curve in Fig. 3) is probably determined by two opposing influences, the increase in available end groups which enhances enzyme activity, and the decrease in the number of chains long enough to be effective which decreases enzyme activity. In Fig. 4 the average chain length of the dextrans at the peak of enzymic activity was found to be close to 5 glucose units which is in agreement with the value found in the experiments with amylose. This suggests that chains of 4 to 3 glucose residues are less effective or

perhaps even ineffective as primers for the potato enzyme.

*Relation of structure to enzyme activation.* While the interpretation of the hydrolysis-activation curves is relatively simple when one is dealing with linear polymers or with unbranched dextrans and can be based on the two opposing effects mentioned above, the situation is more complex in the case of the branched polysaccharides, glycogen and amylopectin. The hydrolysis-activation curves show a much more rapid decline with the muscle than with the potato enzyme and this is consistent with the finding that the potato enzyme can be activated by short-chain dextrans, while the muscle enzyme cannot.

The low activating power of glycogen for the potato enzyme and the marked rise in activating power on short acid hydrolysis cannot be explained

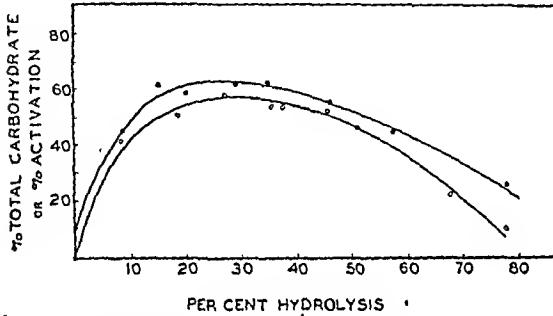


FIG. 4. Effect of products of acid hydrolysis of  $\beta$ -Schärdinger dextrin on activity of potato phosphorylase. Upper curve, enzyme activity with 32 mg. per cent of polysaccharide, expressed in per cent of maximum enzyme activity with 500 mg. per cent starch. Lower curve, concentration of open-chain dextrans during acid hydrolysis in per cent of total carbohydrate.

solely on the basis of available end groups. If that were the case glycogen should initially be more activating than amylopectin, a condition which is true for the muscle enzyme (in proportion to the number of end groups available) but not for the potato enzyme. Such factors as molecular configuration and size of the activating polysaccharide must also play a rôle. The former is indicated by the observation that when the outer branches of amylopectin are removed by the action of  $\beta$ -amylase, the activating power for the potato enzyme becomes very low. The outer branches of glycogen are known to be shorter than those of amylopectin and this may be partly responsible for the difference in activating power of these two polysaccharides for the potato enzyme. With regard to molecular size it would appear that the muscle enzyme is adapted to larger molecules than the potato enzyme.

According to this view glycogen would be nearly optimal in size for the muscle enzyme, since its

activating power increases but slightly on short acid hydrolysis when compared with results obtained with the potato enzyme. The bacterial glycogen of Chargaff which has a particle weight of 12 million would be definitely too large for the muscle enzyme, but as shown in table II, short acid hydrolysis raises its activating power to that of glycogen. The early effect of acid on glycogen may include disruption of hydrogen bonds which would lead to a rapid decrease of particle weight.<sup>3</sup> Finally, amylopectin would be optimal for the potato enzyme, while it cannot be reduced further in size without losing activating power for the muscle enzyme. It is an interesting fact that the particular polysaccharide with which a phosphorylase is in contact in the tissues also has optimal activating power for that enzyme.

*Relation of chain length to iodine color.* When amylose is hydrolyzed in acid, the iodine color changes from blue to purple-blue when about 5 per cent is hydrolyzed; it is purple at 15 per cent and red at 25 per cent hydrolysis. The achromic point is reached at about 30 per cent hydrolysis. Color changes in the reverse order are seen when one starts with partially hydrolyzed Schärdinger dextrans and allows the chain length to be increased by the action of potato phosphorylase. The following table is an example of such an experiment in which there were added per cc. of reaction mixture  $1.57 \times 10^{-6}$  M activating dextrans (calculated as end groups) and  $21.1 \times 10^{-6}$  M glucose-1-phosphate.

time min.	I-ester converted % $M \times 10^{-6}$	average chain length	iodine color
0	0	4.7	0
1.5	3.6	5.2	0
5	8.1	5.8	0
10	16.5	6.9	red
15	27.2	8.3	red
20	32.9	0.1	red
25	38.1	9.8	red
30	39.8	10.0	red-purple
35	44.5	9.4	red-purple
40	48.8	10.35	purple
50	52.9	11.2	purple
60	59.3	12.5	blue-purple
120	73.1	15.5	blue-purple
240	79.4	16.8	blue-purple

The experiment may be regarded as a confirmation of the theory that the action of phosphorylase consists in a lengthening of existing polysaccharide chains. Sumner and collaborators (14) have recently reported an experiment in which a small,

<sup>3</sup> When glycogen is hydrolyzed by  $\alpha$ -amylase, its activating power for potato enzyme reaches a maximum when about 15 per cent is hydrolyzed. The hydrolysis-activation curve with acid is quite different (cf. Fig. 3). In the case of amylose, the hydrolysis-activation curves with  $\alpha$ -amylase or with acid are nearly the same.

intermediate and large amount of an aehroodextrin was added to potato phosphorylase as a priming agent. They found that when an equal quantity of glucose-1-phosphate had reacted, the respective

iodide colors were blue, red or absent, indicating that the chain length of the newly formed polysaccharide is inversely proportional to the number of end groups added with the priming agent.

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## ON THE UTILIZATION AND SYNTHESIS OF SUCROSE AND RELATED COMPOUNDS BY SOME MICROORGANISMS

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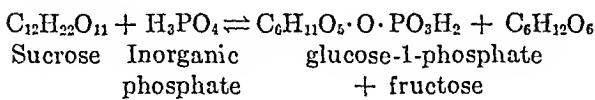
The importance of organic phosphates in catabolism, and of phosphate bond energy as a means of coupling metabolic reactions, is now well recognized. The discovery of the phosphorolytic breakdown and synthesis of glycogen and starch by Cori and Cori, Kiessling and Hanes, has focussed the attention of biochemists on the role of the phosphate esters in synthetic condensation reactions. The findings that sucrose and inosine can also be broken down through reversible phosphorolyses have added the conviction that, in living systems, other syntheses, at least of carbohydrates and their derivatives, may involve similar mechanisms. Some published and as yet unpublished studies with a bacterial enzyme capable of catalyzing the phosphorolysis of sucrose will be discussed in this review. A few pertinent observations on the formation of the polysaccharides dextran and levulan from sucrose by certain bacteria will be considered. The latter studies indicate an alternative mechanism of polysaccharide and sucrose formation, not involving phosphoric esters. Finally, some speculations on the question of how sucrose may be produced by higher plants will be presented, in the hope that they may stimulate some interest in the still obscure problem of disaccharide synthesis in plants and animals.

*Phosphorolysis and synthesis of sucrose.* The

phosphorolytic breakdown of sucrose was first postulated by the Russian scientists Kagan, Latker and Zfasman (1), who observed the accumulation of glucose-1-phosphate in suspensions of the lactic acid bacterium *Leuconostoc mesenteroides* metabolizing this disaccharide. The mode of sucrose utilization by this organism has been the subject of a number of investigations because of its interesting ability to form rather large amounts of the polysaccharide dextran from sucrose, but not from invert sugars. The discovery of the phosphorolysis of sucrose with an entirely different bacterium, *Pseudomonas saccharophila* (2) was made independently and almost simultaneously. The latter organism also exhibits a peculiarity in its carbohydrate metabolism, being capable of oxidizing certain disaccharides and the trisaccharide raffinose more rapidly than the constituent hexoses (3). It was in the hope of explaining this behavior that the search for a phosphorolytic mechanism involved in disaccharide utilization was undertaken. Ironically enough, there is now considerable evidence that phosphorolysis is not involved in dextran formation by *L. mesenteroides*, and does not explain the rapid utilization of disaccharides other than sucrose by *P. saccharophila*. Although the reaction has so far been demonstrated only with these bacteria, it is reasonable to

suppose that the same or related mechanisms will be found to have significance in the metabolic processes of many plants and animals.

While no attempts have been made to prepare the sucrose phosphorylase from *P. saccharophila* in pure form, it has been possible to obtain enzyme preparations virtually free of invertase and phosphatase activity (4). Such preparations catalyse the reaction:

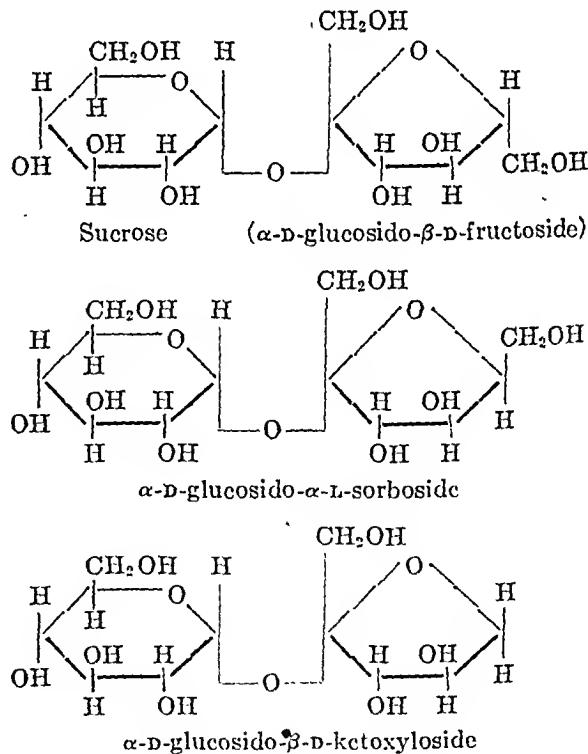


By taking advantage of the reversible nature of the phosphorolytic reaction, the synthesis of sucrose has been accomplished (5). An interesting feature of sucrose formation is that the fructose component of this sugar, as in natural fructose polysaccharides, is found to be in the furanose or five-membered ring form, while free fructose is believed to occur mainly in the pyranose or amylose oxide form. The participation of free fructose in the reaction supports the view that both pyranose and furanose forms exist in equilibrium with each other (6) and makes it unnecessary to postulate that a stabilization of the furanose ring by the formation of a precursor must precede fructoside formation (7).

The bacterial phosphorylase is an adaptive enzyme and is produced in detectable quantity when the bacteria are grown with sucrose or raffinose, but not when they utilize other carbohydrates such as glucose, trehalose, or starch as carbon source. The main course of raffinose decomposition by this organism appears to involve the hydrolytic cleavage of the trisaccharide by an intracellular melibiose to sucrose and galactose, followed by the phosphorolysis of sucrose (8). Hence, the production of sucrose phosphorylase in cultures grown with raffinose as substrate may be considered as a response to the presence of sucrose. The bacterial enzyme does not appear to require a readily dissociable coenzyme or catalytic amounts of sucrose for its activity. Its action, like the phosphorolysis of glycogen, is strongly inhibited by glucose, which, however, seems to compete chiefly with sucrose for a position on the enzyme.

The phosphorylase is quite specific with regard to substrates, and causes no detectable phosphorolysis of starch, maltose, lactose, trehalose, or raffinose. Its inability to attack raffinose indicates that melibiose-1-phosphate cannot replace glucose-1-phosphate in the reverse reaction. Nor have attempts to substitute xylose-1-phosphate or maltose-1-phosphate for glucose-1-phosphate in the reaction with fructose been successful. Fructose cannot be replaced by fructose-6-phosphate,

fructose diphosphate, tagatose, or any of the better known aldose sugars. However, two ketoses, 1-sorbose and D-ketoxylose, have been shown to react with glucose-1-phosphate under the influence of the phosphorylase to form two new analogues of sucrose, unknown in nature (9). In as yet unpublished studies, the new disaccharides have been isolated in crystalline form and found to be non-reducing sugars, easily hydrolysable with acid. Both give the Raybin color reaction characteristic of sucrose (10, 11). For this reason, and because of the presumed specificity of enzyme action, the local structure around the glycosidic bond in these sugars is probably identical with that in sucrose. The results of periodate oxidation indicate that, as in sucrose, the ketose component of both compounds possesses the five-membered ring structure, while the glucose is in the normal pyranose form. This appears to be the first demonstration of the change to a furanose configuration by a ketohexose other than fructose in the formation of a glycoside. Basing the structure of the new disaccharides on the above consideration and on the most generally accepted interpretation of the structure of sucrose, the formulae and designations of the three sugars may be written as follows:



Neither of the new analogues of sucrose is susceptible to hydrolysis with yeast invertase. This indicates that, unlike the sucrose phosphorylase, invertase is very specific for the fructose component of sucrose. On the other hand, the ability of invertase to hydrolyze raffinose shows that it is

less specific than the phosphorylase with regard to the aldose component.

Under suitable conditions, not only sucrose, but also trehalose, maltose, and melibiose are utilized more rapidly than their hexose constituents by *P. saccharophila*. It seemed reasonable to expect a phosphorolytic decomposition of these disaccharides. However, all attempts to demonstrate a phosphorylase for any substrate other than sucrose have failed. The possibility that the phosphorolytic decomposition might involve not the disaccharides themselves but their phosphoric esters, which could be formed through a preliminary phosphorylation, was also investigated. The remarkable similarity of the utilization of trehalose to that of sucrose by the living organisms (3, 12), the structural relationship of the two sugars, and the occurrence of trehalose phosphate in yeast (13) made trehalose a particularly promising substrate for such studies. The experimental evidence, however, has not supported the view that phosphorolysis may play a role in the decomposition of trehalose or of any disaccharide other than sucrose by the bacterium. This evidence, partly unpublished, may be summarized as follows:

1. No phosphorylase other than sucrose phosphorylase has ever been demonstrated, while intracellular hydrolytic enzymes capable of attacking the substrate are present.

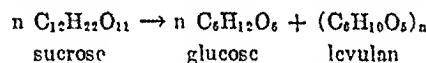
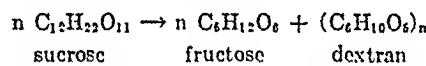
2. The internal accumulation of a labile ester having the properties of glucose-1-phosphate can be shown readily *in vivo* when the bacteria are oxidizing sucrose (8). No such ester formation occurs with trehalose or melibiose.

3. A small amount of hexokinase activity could be shown in dry cell preparations of bacteria grown with trehalose. That these preparations contained no special enzyme for phosphorylating trehalose was shown by the fact that the transfer of phosphate from adenosine triphosphate was, if anything, slower rather than greater when the disaccharide was supplied in place of glucose.

*Dextran and levulan formation.* While the reversible nature of the phosphorolytic reactions with starch, sucrose, and inosine has given us an indication of how some complex carbohydrates may be synthesized in organisms, another mechanism of synthesis, which apparently does not involve phosphoric esters, deserves special attention, since it may be the basis of the production of many carbohydrates of biological importance. This mechanism appears to be the exchange of an already existing glycosidic linkage for a new glycosidic linkage. The formation of polysaccharides through what appears to be such a reaction has been observed in the bacterial synthesis of dextran and levulan from sucrose. Dextran, which is a polymer of glucose in which the hexose units are joined through a 1-6 linkage, is produced in large

quantities by *L. mesenteroides* when the latter is grown with sucrose, but not with invert sugar (14, 15). An immunologically identical compound is found in the polysaccharide capsule of some of the Pneumococci (16, 17). Levulan, a fructose polymer having the 2-6 linkage, is known to be formed abundantly by many species of *Bacillus* (14), one of *Acrobacter* (18) and two of *Streptococcus* (19) in the decomposition of sucrose or raffinose, but not of hexoses. It is interesting that a very similar or identical substance appears in large amounts in barley and in certain wild grasses (20, 21). In the bacteria, dextran and levulan syntheses may be regarded as being analogous to capsule formation, however, the abundance and solubility of the material causes it to accumulate in the medium instead of remaining in close association with the cell.

While in some cases, the enzymes responsible for the polysaccharide production appear mainly within the cell, in the *Bacilli*, and in at least some strains of *Leuconostoc*, they may diffuse into the medium. Hechre's (16, 17, 22), as well as Hestrin and Avinieri-Shapiro's experiments (18) with cell-free enzyme preparations have shown that the formation of neither dextran nor levulan requires any organic or inorganic phosphate, and that the processes may be written as follows:



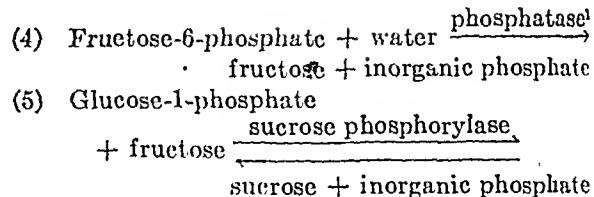
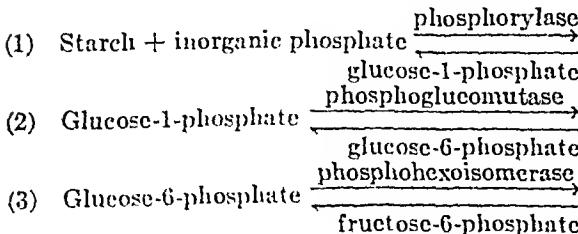
In the case of levulan synthesis, either sucrose or raffinose may act as substrate, the radical attached to the fructose portion being set free as glucose or melibiose respectively. In addition to the reaction leading to levulan synthesis, what appears to be a hydrolytic decomposition of sucrose and raffinose usually takes place. Hestrin and Avinieri-Shapiro have tried to write a single equation accounting for the products of both reactions. They found that the ratio of substrate used for synthesis to that hydrolyzed was approximately unity. However, as they themselves point out, the relation between the two processes is not obvious, and, indeed, is difficult to visualize. In experiments with extracellular enzymes of *Bacillus subtilis* (23), no rigid relationship between levulan formation and inversion of sucrose could be found. The ratio of the products was found to vary depending on the age of the culture from which the enzymes had been obtained, and on the conditions of incubation of the preparations. Although Hestrin and Avinieri-Shapiro showed that the presence of glucose retards the synthesis of levulan, they were unable to demonstrate the reversible nature of levulan

formation. Indirect evidence of the reversibility of the process has been obtained recently with cell free concentrates and precipitated preparations from *Bacillus subtilis* (23).

It was assumed that the principal difficulties in showing the reaction from right to left lie in the high molecular weight and therefore relatively low concentration of the polysaccharide, and in the presence of insufficient invertase in the preparations to remove sucrose as it is formed.

To displace the equilibrium to the left, yeast invertase was added to the bacterial enzyme. In such a system, the addition of glucose markedly increased the decomposition of levulan to reducing sugar. No similar effect of glucose could be detected either with the bacterial enzyme alone or with invertase alone. As in the other reported studies, no effect of phosphate on the reaction in either direction could be observed. This indirect evidence that the formation of levulan depends on a reversible reaction, in which the glycosidic bond of sucrose is exchanged directly for the glycosidic bond of fructosan, indicates a new mechanism of sucrose synthesis through the reaction from right to left. Presumably, sucrose would also be formed under the influence of the appropriate enzyme from fructose and dextran, although the reversibility of dextran synthesis has not yet been tested experimentally. From these considerations, it would seem that the residues of at least some glycosides can serve a function similar to that of the phosphoric ester group of glucose-1-phosphate in the formation of complex carbohydrates. The exchange of glycosidic bonds may play an important rôle in the synthesis of a variety of polysaccharides.

*On the possible mechanisms of sucrose production by plants.* The synthesis of sucrose with bacterial phosphorylase raises the question of whether the formation of this sugar in the tissues of higher plants is the result of an identical or a similar process. That widely different organisms exhibit remarkable similarities in their metabolic mechanisms is one of the basic concepts of comparative biochemistry. It is therefore tempting to speculate that sucrose might arise from starch in the ripening of many fruits and on cold storage of potatoes through the following series of known reactions:



The transformation of hexose sugars to sucrose, which can readily be observed *in vivo* in many plants, would, of course, involve their phosphorylation and subsequent participation in the above scheme.

Although our knowledge of the metabolic activities of high plants is extremely meager, it seems fair to postulate that the enzymes necessary for the first four steps in the above series of transformations are of rather general distribution. However, the following three objections may be raised against the probability of the occurrence of the fifth step in higher plant tissues:

- (1) All attempts to demonstrate a sucrose phosphorylase in plant extracts and macerates have so far failed.
  - (2) The formation of sucrose from starch appears to depend on respiratory activity.
  - (3) The high concentration of sucrose observed in some plants is incompatible with the equilibrium constant for the phosphorolytic process.

The first objection is the least valid, since it is well known that many enzymes are difficult to demonstrate. Numerous unpublished experiments with sugar beets, sunflower leaves, ripening bananas, potatoes, and a variety of other materials have yielded uniformly negative results. This may, of course, be due to the labile nature of the plant phosphorylase or to the dependence of its activity on some structural or physiological feature of the intact cell. However, the ease of extraction and the relative stability of the plant starch phosphorylase and of the bacterial sucrose phosphorylase make such an explanation less likely than in the case of some other enzymes.

It is not surprising that the interconversion of glucose and fructose, as well as the formation of sucrose from either of these sugars, requires respiratory activity (24, 26) since phosphorylation of the hexose would be required before its transformation or condensation could be accomplished through recognized or postulated reactions. However, the proposed scheme of sucrose formation from starch requires no external energy source, and is therefore contradicted by the observation

<sup>1</sup>This hydrolytic reaction is practically irreversible, since, in addition to the energy changes involved, the high concentration of water as one of the reactants favors the reaction from left to right.

that no sucrose is formed in intact bananas and potatoes when these are kept under anaerobic conditions (25-28). This respiratory requirement suggests that an energy-rich compound must be generated before sucrose can be formed. Such a compound might be a hexose phosphate other than glucose-1-phosphate or its derivatives, glucose-6-phosphate and fructose-6-phosphate. The probability that fructose diphosphate plays a rôle in sucrose synthesis by sugar cane has been strongly advocated by Hartt (29).

The most serious objection to the proposed scheme is that sucrose occurs in some plants in extremely high concentrations. During the ripening of bananas, for example, the starch is almost completely converted to the disaccharide. The equilibrium constant for the phosphorolytic reaction, expressed as

$$K = \frac{(\text{sucrose})(\text{phosphate})}{(\text{glucose-1-phosphate})(\text{fructose})}$$

was found to be in the neighborhood of 0.05 at pH 6.6 at 30° (4). The concentration of glucose-1-phosphate in plants is extremely small, while inorganic phosphate often occurs in relatively large amounts. Yet it is common to find many times as much sucrose as fructose in plant tissue. In order to accept the phosphorolytic condensation of glucose-1-phosphate and fructose as the possible mechanism of sucrose formation in plants, we would therefore have to assume that the sucrose is somehow selectively removed from the site of synthesis, so that the reaction may proceed. The removal of inorganic phosphate, which might be accomplished by local respiratory activity would not alone be likely to have much significance, since it would also prevent the local phosphorolysis of starch.

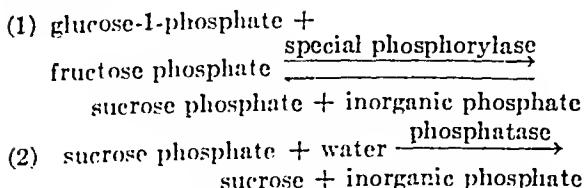
It seems appropriate at this point to consider various other possible mechanisms for sucrose production which might be looked for in plants and which would not be open to the criticisms suggested above. The possibility that sucrose arises by direct reaction between starch and fructose, similar to that between levulan and glucose, can be objected to on the same grounds as the phosphorolytic process. The elimination of glucose-1-phosphate as an intermediate would not change the equilibrium of starch, fructose, and sucrose. The difficulty of demonstrating by other than indirect means the reversible nature of levulan synthesis indicates that such reactions are not likely to be useful for the production of sucrose in high concentration. From the above considerations, it will be seen that a chain of completely reversible reactions without a special mechanism for the removal of any of their products would result in the accumulation of starch rather than sucrose as the

principal carbohydrate of the cell, while the occurrence of an irreversible step leading to the formation of a hexose such as postulated in reaction (4) would favor the production of the monosaccharide. It therefore seems quite probable that the mechanism of sucrose formation in plants involves at least one practically irreversible reaction leading directly to the synthesis of the disaccharide. It is difficult to visualize a mechanism for glycoside formation in which a bond of much higher energy than the glycosidic ester bond would be directly involved, or in which the energy from two such bonds could be used for the synthesis. A more likely possibility suggests itself as fulfilling the requirement for virtual irreversibility, namely the hydrolytic decomposition of an immediate precursor of sucrose which would, in effect, remove sucrose from any chain of reversible reactions. Both the high concentration of sucrose found in some plants and the respiratory requirements for its synthesis can be reconciled with the postulation of such a hydrolytic decomposition or an equivalent of this process, if it is assumed that the precursor is sucrose phosphate. For the formation of such a compound, phosphorolysis of starch might not be sufficient, and additional phosphorylations may be required. While sucrose phosphates have never been isolated from living tissues, the demonstration of the occurrence of trehalose phosphate in yeast (13) indicates that such compounds may play a rôle in metabolism. The chemical synthesis of a sucrose phosphate has been accomplished and the synthetic compound has been shown to be susceptible to phosphatase activity (30-32).

Several schemes have been proposed in which sucrose phosphate is assumed to arise through the condensation of phosphoric esters of glucose and fructose (7, 25, 29, 33, 34, 37). The claims of Oparin and Kursanov that sucrose could be synthesized from invert sugar in the presence of phosphate through the combined action of invertase and phosphatase could not be confirmed (35). Such a mechanism would be most unlikely, since it would depend on the reversible nature of two practically irreversible hydrolytic reactions. Hartt's recent scheme (29) in which sucrose phosphate would arise through the condensation of glucose with fructose diphosphate offers no plausible mechanism for the formation of the glycosidic linkage. In effect, such a scheme again requires the reversal of a hydrolytic reaction as the basis of the condensation. It is difficult to see how the presence or the removal of a phosphoric acid group from either the first or the sixth carbon atom of fructose diphosphate would result in a reaction involving the second carbon atom, although from the point of view of energetics the dephosphorylation would facilitate such a reaction. Hartt's speculations on

the possible rôle of thiamin and riboflavin as phosphate acceptors in the formation of sucrose from hexose phosphates, based on the experimental observation that the addition of these vitamins increases sucrose synthesis, are open to several criticisms. Her implication that a release of inorganic phosphate should be observed during the ripening of sugar cane if the phosphate is not transferred to an organic acceptor is not valid, since presumably sucrose phosphate would never accumulate in high concentration, and since obviously no phosphorylated compound like cocarboxylase could be one of the chief end products of sucrose synthesis. Furthermore, only the ester phosphate, and not the pyrophosphate radicals could be formed by such transfers, since the latter require a donor of much higher energy than the sugar esters. Finally, if a release of phosphate bond energy is required for glycoside formation, the removal of phosphate through a reaction involving little or no energy change would prevent rather than facilitate the coupling reaction. The last consideration, however, is not meant as an argument against the possible existence of a phosphate acceptor which might participate in the production of sucrose from a hypothetical sucrose phosphate after the formation of the glycosidic bond.

A more plausible scheme for the formation of a phosphoric ester of sucrose than those already considered would involve a phosphorolytic condensation similar to that observed with the bacterial enzyme, but differing in the nature of the reacting substances. This would require the presence of a phosphate radicle on the carbonyl atom of one of the reactants and at least one additional phosphate group in another position on either of the two. It seems reasonable to suspect that in such a case, glucose-1-phosphate would play a rôle in the condensation, since very strong starch phosphorylase activity can be observed in ripening bananas and other plant tissues in which starch can be converted to sucrose. It seems hard to believe that an existing mechanism for glycoside formation would not be used for that purpose. If a plant phosphorylase were capable of condensing glucose-1-phosphate with a fructose ester, such as fructose-6-phosphate or fructose diphosphate, but not with the unphosphorylated sugar, then sucrose synthesis might proceed according to the following scheme:



If the fructose ester were fructose-6-phosphate, this scheme would not necessarily require addi-

tional phosphorylation, since this compound can arise from glucose-1-phosphate. If, on the other hand, this compound were fructose diphosphate, the need for an outside source of energy would be understandable, provided this ester does not originate by the transfer of ester phosphate from one molecule of hexose monophosphate to another (36). If such a transfer does occur, the transformation of starch to sucrose diphosphate in the absence of phosphorylation is theoretically possible, but only two-thirds of the starch could be so converted, one third being lost as free hexose. Neither of the fructose phosphates can replace fructose as substrate for the bacterial sucrose phosphorylase. This, however, cannot be used as an argument against the above scheme, since the postulation of a mechanism for the irreversible synthesis of sucrose would require a high degree of specificity in the enzyme catalyzing the phosphorolytic condensation of the two phosphoric esters. Such an enzyme would not be identical with bacterial sucrose phosphorylase. A number of plant extracts and macerates have been tested for their ability to condense glucose-1-phosphate with the known fructose phosphates. In no case has it been possible to demonstrate such a reaction, but this fact does not preclude the possibility of its occurrence, since a number of factors complicating such studies have not yet been eliminated.

Another possibility which must be investigated is that the formation of sucrose phosphate depends on the occurrence of an as yet unknown phosphoric ester of glucose or fructose. Such a compound might arise through the phosphorylation of glucose-1-phosphate with the formation of a diphosphate, or through the phosphorylation of fructose on the second carbon atom. Sucrose phosphate might also be formed through the reaction of glucose-1-phosphate with a triose phosphate and the subsequent addition of another triose phosphate.

The occurrence of a sucrose phosphate is not, however, essential for a scheme in which sucrose can be formed through an irreversible decomposition of an immediate precursor. Any radical attached to either the glucose or the fructose moiety in any position not involved in glycoside formation could fulfill a function similar to that of an additional phosphate. After the formation of glucosido-fructoside linkage, sucrose could be formed by removal of such a radical directly by hydrolysis. Alternatively, the attached group could be transferred to some acceptor, which, in turn, could be regenerated by hydrolytic decomposition. Such a scheme is, of course, entirely hypothetical, but can be illustrated in principle by the hydrolytic production of sucrose from the trisaccharide raffinose. If galactosido-glucose (melibiose)-1-phosphate were to react with fructose to form raffinose, the

latter could then be decomposed to sucrose and galactose by the action of melibinase. In view of the occurrence of glucose-1-phosphate in some sucrose forming tissues, it might be more profitable to look for a compound of fructose rather than of glucose involved in such a condensation and hydrolysis.

The foregoing considerations of the possible mechanisms of sucrose synthesis in plants might also apply to the problem of the production of polysaccharides and disaccharides other than sucrose in plants and animals. The formation of lactose in the mammary gland, for instance, has not as yet been accomplished with maceerates or extracts, although it can be observed with respir-

ing tissue slices. In conclusion, it may be said that the key to the formation of many disaccharides and polysaccharides seems to be near discovery, but has in most cases eluded a direct approach up to the present time. The role of the exchange of phosphoric ester bonds for glycosidic linkages, and of the exchange of glycosidic bonds themselves, have given a clue to the types of reactions to be sought in carbohydrate syntheses. The mechanism of sucrose synthesis in plants seems to be one of the most promising reactions for study. Its understanding would contribute greatly to the elucidation of a number of related processes.

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## ENZYMATIC SYNTHESIS OF NUCLEOSIDES

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The nucleosides which constitute the building units of nucleic acids are ribosides in which the aldehyde group of the ribose (or desoxyribose) is linked to one of the nitrogens of the purine or pyrimidine ring. This linkage, like all glucosidic linkages, is very stable toward alkali but more or less labile to acid.

The ribosidic linkage in nucleosides is split by certain enzymes called nucleosidases which have been found mainly in liver, spleen (1) and in milk (2). Klein (3) reported about ten years ago that nucleosidases from liver and spleen were inactive unless phosphate or arsenate was present. The mechanism of this interesting effect was not studied, however, and very little work has been conducted since in that field.

In the experiments to be presented here, emphasis was placed on giving a complete account of the fate of the purine component as well as of that of ribose and phosphate during enzymatic splitting of nucleosides. The nucleosidase used was prepared from rat liver by high speed centrifugation, fractionation with ammonium sulfate, and isoelectric precipitation. The enzyme obtained was a nucleosidase, or presumably two nucleosidases, which catalyze the splitting of inosine and guanosine, i.e. they split the ribosidic linkage between hypoxanthine, or guanine, and ribose. Before proceeding to a presentation of the results obtained, it might be useful to mention briefly the methods employed in these studies.

*Methods.* Hydroxy- and amino-purines (free or bound as ribosides) were determined by a new technique in which changes in the intensity of absorption of ultraviolet light at certain wavelengths were brought about by specific enzymes (4). Hypoxanthine, for example, was oxidized to uric acid by addition of xanthine oxidase. This reaction causes a very considerable increase in the absorption at 290 m $\mu$  at which wavelength uric acid has its maximum absorption. At 248 m $\mu$  the change in absorption by oxidation of hypoxanthine via xanthine to uric acid is the reverse of that at 290 m $\mu$ , i.e. the absorption is decreased to about half of the original value. The decrease in absorption at 248 m $\mu$  actually occurs solely in the first step of the oxidation, i.e. from hypoxanthine to xanthine. The oxidation of xanthine to uric acid (the second step) involves no change in absorption at this wavelength but brings about an increase at 290 m $\mu$  and, in addition, a marked decrease in absorption at 270 m $\mu$ . By measuring optical changes at

these three wave-lengths it is possible to distinguish between hypoxanthine, xanthine and uric acid. Guanine is determined by the changes in density at 290 and 270 m $\mu$  brought about by adding guanase plus xanthine oxidase. Table 1 summarizes the changes in extinction at various wavelengths as referred to 1  $\mu$ g. of the purine base per ml.

Inosine (hypoxanthine riboside) is not attacked by xanthine oxidase. In order to determine this compound, liver nucleosidase (in phosphate buffer) was added together with xanthine oxidase. The nucleosidase causes a liberation of hypoxanthine which is subsequently oxidized to uric acid. If phosphate is present in high concentrations or if the xanthine oxidase is present in excess so as to remove the hypoxanthine formed, the splitting of the riboside goes to completion in less than thirty

TABLE 1  
*Optical microtests for purines*

PURINE BASE 1 $\mu$ G. PER ML.	ENZYMES USED	DENSITY CHANGES ( $\pm \Delta \log \text{E}_\text{o}/\text{i}$ ) AT VARIOUS WAVELENGTHS		
		290 m $\mu$	270 m $\mu$	248 m $\mu$
Hypoxanthine.....	Xanthine oxidase	+0.081		-0.030
Xanthine.....	Xanthine oxidase	+0.066	-0.053	
Guanine.....	Xanthine oxidase + Guanase	+0.060	-0.030	

minutes. The addition of xanthine oxidase serves actually two purposes: (i) It removes one of the primary enzymatic split products formed from inosine (i.e., hypoxanthine) and (ii) it is used as an analytical tool for the determination of liberated hypoxanthine due to the optical changes caused by its oxidation to uric acid. Inosine nucleosidase, in the presence of xanthine oxidase and an excess of inorganic phosphate, likewise serves as a highly sensitive and specific tool in the determination of hypoxanthine riboside. By making use of the principles just outlined, it is possible to determine hypoxanthine and inosine with great accuracy in a mixture of both components.

To summarize, the amount of free hypoxanthine present in the mixture is determined by the optical changes brought about by addition of xanthine oxidase; the amount of inosine is determined by the increase in density which accompanies a fur-

ther addition of inosine nucleosidase. Guanosine is estimated according to the same principles, using nucleosidase, guanase and xanthine oxidase as analytical aids. The liver nucleosidase preparations used contain guanase. In spite of this, guanine and guanosine can be determined independently due to the fact that guanase is active in the absence of phosphate, whereas guanosine nucleosidase is active only in the presence of phosphate.

Phosphate was determined by a new method devised by Lowry (5). The advantage of this method over previous ones is that it is performed at a weak acid reaction (pH 4.2 to pH 4.6). This makes it possible to determine genuine inorganic phosphate in the presence of highly acid labile phosphoric esters. It will be understood from what follows

TABLE 2  
Enzymatic splitting of inosine in the presence of xanthine oxidase

Substrates: 125 µg. inosine + 25 µg. P or (for control experiments) 90 µg. hypoxanthine + 100 µg. d-ribose + 25 µg. P.

Enzymes: Liver nucleosidase (20 µg.) + xanthine oxidase (30 µg.).

Buffer:  $\frac{M}{10}$  glycyl-glycine pH 7.2. Gas: oxygen. Temperature: 27°.

SUBSTRATE	MIN. INCUB.	URIC ACID µ MOL	PHOSPHORUS	
			µ g. P	µMOL P UTIL- IZED
Inosine.....	0	0	13.0	
Inosine.....	80	0.25	4.5	0.27
Hypoxanthine + Ribose....	0	0	13.6	
Hypoxanthine + Ribose....	80	0.27	13.0	0.02

why this modification has been of importance for the present studies. The pentose was determined quantitatively by the orcinol test (6) and the aldose by oxidation with iodine and titration with thiosulfate (7).

*Participation of Inorganic Phosphate in the Enzymatic Splitting of Inosine and Guanosine.* By means of the methods just outlined, the following observations were made: (i) The enzymatic splitting of inosine and guanosine takes place only in the presence of phosphate or arsenate; (ii) phosphate is utilized during the enzymatic splitting; (iii) one mol of phosphate is taken up per one mol of purine base liberated; (iv) in the absence of xanthine oxidase the enzymatic splitting of inosine does not proceed very far except when the concentration of inorganic phosphate is many times higher than that of the nucleosides. Thus, 0.38 µmols of inosine plus 0.37 µmols of phosphate incubated with liver nucleosidase yielded 0.031 µmols of hypoxanthine and 0.033 µmols of P were taken up. In other words,

only 10 per cent of the inosine undergoes splitting and the reaction does not proceed farther if the incubation time is extended.

If, on the other hand, the hypoxanthine, as it is liberated, is oxidized to uric acid, by adding xanthine oxidase to the nucleosidase, the splitting proceeds almost to completion and the amount of phosphate utilized is equivalent to the amount of uric acid formed (table 2). The lack of phosphate uptake in the samples incubated with hypoxanthine plus ribose, which showed the same oxygen uptake as the samples incubated with inosine, proves that the nucleoside linkage is essential for the uptake of phosphate.

The same type of experiment can be performed with guanosine, i.e., the liver nucleosidase is able to split guanosine provided inorganic phosphate is added. The phosphate is taken up in organic linkage. Since the liver nucleosidase used contained guanase the guanine liberated was found in the form of xanthine (table 3). It can be seen that one mol P is taken up for each mol xanthine formed.

TABLE 3

*Splitting of guanosine by liver nucleosidase*

85 µg. guanosine (corresponding to 45 µg. guanine) were incubated in the presence of phosphate (20 µg. P).

Liver nucleosidase was added as enzyme. Incubation time 40 minutes at 30°.

	µG.	µmols
Purine (as xanthine) formed.....	26.8	0.175
P taken up.....	5.2	0.168

*Formation of Ribose-1-Phosphate.* It has been possible to isolate a hitherto unknown phosphoric ester by incubating larger amounts of inosine with xanthine oxidase (to which was added a small amount of crystalline catalase to prevent any accumulation of hydrogen peroxide) plus liver nucleosidase and an excess of inorganic phosphate. This ester which was obtained as a barium salt shows the following properties. The phosphate group is very readily split off in acid medium even at room temperature. Thus, incubation of the ester in 0.3 normal hydrochloric acid at 30° causes a splitting of 40 to 50 per cent of the labile phosphate in one minute, and in fifteen minutes all the labile phosphate has been converted into inorganic phosphate. Due to its extreme lability the ester cannot be determined by the ordinary phosphate methods which operate at a strongly acid reaction, but it can readily be determined by Lowry's modification which operates at weak acid reaction. The ester can also be determined by the difference between the amount of phosphate estimated directly

by Fiske's reagent and phosphate precipitated by ammonium magnesium mixture, since it is fairly stable in alkali at room temperature.

The substance was found to be a pentose phosphoric ester; a sample containing 3.2  $\mu\text{mol}$  pentose yielded 3.3  $\mu\text{mol}$  aldose and 3.6  $\mu\text{mol}$  inorganic phosphate after acid hydrolysis.

The phosphate must be in the 1-position, i.e. on the aldehyde group since the ester is non-reducing, in analogy with glucose-1-phosphate (Cori ester (8)). Inasmuch as the ester is formed from a ribose nucleoside it is considered to be a ribose ester and will be referred to as ribose-1-phosphate, although it should be emphasized that it remains to be shown whether the pentose component is *d*-ribose, and if so, whether it is an alpha or a beta ester. Ribose-1-phosphate can also be formed from guanosine and phosphate in the presence of liver nucleosidase.

*Enzymatic Synthesis of Inosine and Guanosine.* Ribose-1-phosphate seems to be a key substance in the biological synthesis of ribose nucleosides. This is borne out by the following experiments. If ribose-1-phosphate is incubated with hypoxanthine in the presence of liver nucleosidase a rapid synthesis of nucleoside (inosine) takes place. The experiment described in table 4 illustrates such a synthesis.

The reaction does not take place if ribose plus phosphate, or if glucose-1-phosphate is substituted for ribose-1-phosphate.

Guanine reacts with ribose-1-phosphate in the presence of the liver nucleosidase much in the same manner as does hypoxanthine (table 5). The conversion of guanine and ribose-1-phosphate to guanosine might proceed almost as far as in the case of the corresponding synthesis of inosine. However, due to the presence of guanase a part of the guanine is "sidetracked" and converted into xanthine. It is important to emphasize that xanthine itself is inactive in the test. This eliminates the possibility that guanine acts by being deaminated to xanthine. Likewise, adenine shows no activity in the test.

*The Equilibrium of the Reaction.* It was already stated that incubation of equimolar amounts of inosine and phosphate with the enzyme causes only ten per cent of the nucleoside to undergo cleavage. Table 4 which illustrates the reverse reaction shows that 80 per cent of the cleavage products react to form the nucleoside. Since almost all preparations of ribose-1-phosphate contain some inorganic phosphate (10 to 20 per cent of the phosphate is usually inorganic) the degree of nucleoside synthesis is always somewhat underestimated. The position of the equilibrium at pH 7 is probably at a point where approximately 10 per cent of the participants exist as free hypoxanthine and ribose-1-phosphate, and 90 per cent as inosine

and inorganic phosphate. The exact position of the equilibrium in the corresponding reaction with guanine cannot be stated until the nucleosidase is free from guanase (see Addendum).

TABLE 4  
*Enzymatic synthesis of inosine*

0.58  $\mu\text{mols}$  hypoxanthine (78  $\mu\text{g}.$ ) plus 0.58  $\mu\text{mols}$  ribose-1-phosphate (15.5  $\mu\text{g}.$  labile P) were incubated with liver nucleosidase. In the controls, one of the components was omitted during the incubation and added after denaturation of the protein. In Sample 1, ribose-1-phosphate was omitted; in sample 4, hypoxanthine, and in 5, nucleosidase were absent during the incubation (40 minutes). Samples 2 and 3 represented the complete system incubated 20 and 40 minutes respectively.

SAMPLES	INORGANIC P	HYPOXANTHINE	INO-SINE (AS HYPOXANTHINE)	P LIBERATED	HYPOXANTHINE REMAINING	INO-SINE FORMED
	$\mu\text{g.}$	$\mu\text{g.}$	$\mu\text{g.}$	$\mu\text{mols}$	$\mu\text{mols}$	$\mu\text{mols}$
1 (Control).....	9.8	72	0	0	0.53	0
2-Complete, incubated 20 minutes.....	22.1	13.3	53.5	0.32	0.10	0.39
3-Complete, incubated 40 minutes.....	23.4	14.3	51.0	0.30	0.11	0.38
4 (Control).....	9.8	71.5	0	0	0.53	0
5 (Control) .....	9.8	69	0	0	0.51	0

TABLE 5  
*Enzymatic synthesis of guanosine*

0.28  $\mu\text{mols}$  of guanine were incubated with liver nucleosidase. 0.25  $\mu\text{mols}$  of ribose-1-phosphate were added. In the control the ribose-1-phosphate was added after the denaturation of the enzyme. In the experimental sample the ribose-1-phosphate was incubated with the guanine in the presence of cymne. Incubation time 20 minutes. Temperature 30°.

	CONTROL SAMPLE	EXPERIMENTAL SAMPLE
$\mu\text{mols}$ guanine remaining.....	0.12	0.13
$\mu\text{mols}$ xanthine formed.....	0.16	0.10
$\mu\text{mols}$ guanosine synthesized.....	0	0.05

From all that has been said, it is therefore clear that the splitting of inosine and guanosine by liver nucleosidase is not hydrolytic but phosphorolytic. It is therefore suggested that the enzymes which catalyze the reversible reaction be called nucleo-

side phosphorylases in analogy with Cori's polysaccharide phosphorylase (9) and Doudoroff's disaccharide phosphorylase (10). The reaction can be formulated by the following equation (11): Ribose-1-purine (purine nucleoside) + phosphate  $\rightleftharpoons$  ribose-1-phosphate + purine. The purines involved are hypoxanthine and guanine, the nucleosides participating in the reaction being inosine (ribose-1-hypoxanthine) and guanosine (ribose-1-guanine). Most likely inosine and guanosine nucleosidase are two independent enzymes, but at the present time the enzyme activities have not been separated, and it is conceivable that the two activities might arise from the same enzyme. Neither is it possible to make definite statements about the absence of xanthosine nucleosidase in liver. If the liver is unable to incorporate xanthine into ribosides, the reduction or the amination of xanthine become preliminary steps in the formation of purine nucleosides from xanthine.

Colowick and Price (12) have most recently discovered a very interesting reaction in which guanine is liberated from a large molecular compound, presumably nucleic acid, by a phosphorolytic enzyme from muscle. The guanine liberated acts as an activator in the enzymatic phosphorylation of glucose by adenosine triphosphate.

There is reason to believe that phosphorolytic enzymes may be of wide significance in the metabolism of every type of nucleoside. The pyrimidine nucleosidase from bone marrow (13) deserves attention in this regard. So does the enzyme which catalyzes the splitting of nicotinamide from reduced cozymase (14). Both these enzymes have been considered important in the destruction of nucleosides; yet they may turn out to be of great importance for the synthesis of pyrimidine and nicotinamide nucleosides.

Ribose-1-phosphate may be the precursor in all reactions in which ribo-nucleosides are synthesized. The problem of how new nucleosides are formed is therefore linked up with the problem of whether ribose-1-phosphate can be formed in any other way than by phosphorolysis of already

existing nucleosides. Phosphorolysis can only give rise to transfer and exchange of purines in nucleosides or nucleic acids. However, in order to form new nucleosides it is necessary to form ribose-1-phosphate by phosphorylation of free ribose just as glucose-1-phosphate can be formed not only from polysaccharides, but also from glucose by phosphorylation in the 6-position with subsequent enzymatic migration of the phosphate group to the 1-position (15). The problem of how new nucleosides can be synthesized may be complex and it may prove to be impossible to treat it separately from the problem of how ribose is formed in the animal organism. Is this sugar formed from hexoses or by an aldol condensation of triose and glycol aldehyde? There are observations which favor the latter assumption (16).

There are many interesting aspects as to what role nucleosides might play in the metabolism and in the growth of living cells. It may be worthwhile to point out that although it is believed that most cells are capable of synthesizing a large number of nucleosides, it is not impossible that this synthetic capacity may under certain conditions become a limiting factor. It has for instance been found (17) that pyrimidine-deficient mutants of *Neurospora* do not respond to the addition of pyrimidines to the medium but show a marked response if pyrimidine nucleosides are added. In the animal organism the liver probably plays the most important rôle in the synthesis of purines and purine nucleosides. It is quite conceivable that when the liver function is disturbed and there is simultaneously a great need for synthesis of nucleic acids (e.g. conditions such as pregnancy, growth, tissue repair) the rate of formation of nucleosides or of ribose phosphate may become one of the limiting factors.

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*Addendum:* It has recently been possible to obtain nucleosidase free of guanase, using pig liver. Moreover it has also been possible to free nucleosidase from rat liver of guanase by adsorbing the latter on barium sulphate. If guanine and ribose-

1-phosphate were incubated with nucleosidase preparations which were free of guanase almost half of the guanine was found to be incorporated in nucleosidic linkage giving rise to the formation of substantial amounts of guanosine.

*The American Institute of Nutrition*  
**SYMPOSIUM ON NUTRITION SURVEYS**  
**INTRODUCTION**

C. G. KING, *Chairman*

*Scientific Director, The Nutrition Foundation, Inc.*

The primary purpose of the symposium is to bring before the members of the Federation reports of techniques and findings that characterize outstanding recent nutrition surveys in the United States, and to provide an opportunity for each of the speakers to present something of his viewpoint in regard to the value of such surveys.

We have asked each participant to present a brief account of what has been observed in the way of factual evidence, to comment upon the significance of the findings in his respective area, and to indicate something of his plans for future work.

In organizing the program, we have been essentially looking forward rather than backward. Hence, we trust there will be a continuing emphasis upon: first, the need for improved techniques of study; second, the securing of a clearer picture of the relation of nutrition to health; and, third, the development of education and public health services in such a way that the public can benefit in maximum degree from the scientific advances as they are made.

The most serious need in regard to human nutrition is still basic information, or research, but there should be no doubt of the value of nutrition surveys as a means of evaluating "where we stand" with respect to accomplishing the goal of a well nourished population.

From the point of view of maintaining a vigorous home front during the war and for the purpose of raising our normal level of public health, it is important that surveys of many types be conducted at frequent intervals. Especially should it be emphasized that food production and distribution programs cannot be well directed without the kind of information that nutrition surveys can provide.

One may say with some truth that the techniques of conducting surveys still leave much to be desired, but that is true of almost every area of research and technology. Estimates of individual food intake, in terms of specific nutrients

and food commodities, can be achieved in a relatively satisfactory manner. Many indices of mild and severe nutritive deficiencies are also available for clinical usage in securing valuable information. And even though much is to be desired concerning agreement among clinicians with respect to the specificity of nutritional deficiency lesions, it would be foolish indeed not to make use of the information that clinical examinations can provide. Again, there is a great need for better appraisal of the health significance of different degrees of tissue storage of specific nutrients, but on the whole, chemical data of this nature give increasingly valid measures of nutritive status; the evidence is more objective than most types of observation on the condition of an individual, and the techniques are applicable to a wider range of nutritional levels—especially in regard to the lesssevere forms of deficiency where there are no well defined lesions.

Depending upon the purpose, some surveys need to be of short duration and others need to be carried out recurrently over a number of years. In Britain, for example, "spot surveys" have proved to be very valuable in following trends in food consumption. We have needed more information of that kind here.

At the other extreme, and bordering on what many would call research rather than a survey type of study, *perhaps the most seriously needed type of related study in America is to find, through long periods of time, the degree of correlation that exists between the health records of individuals and their dietary habits.* Information of that kind would probably astound many of the nutritionists, even, and should provide powerful weapons with which to combat the widespread complacency and uncertainty regarding the real significance of our various food consumption practices.

Each contributor to the symposium has rendered outstanding service to the development of nutrition surveys, in one or more of the respective areas just referred to.

## TECHNIQUES OF FINDING OUT WHAT PEOPLE EAT

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The techniques involved in studies of what families and individuals eat are determined by the primary purpose to be served by the resulting information, whether sociological, physiological, or economic. Rarely is a study useful for only one purpose, but the main objective of the study will affect the methods selected and the use to which the final results can be put. Outlined here are some of the methods commonly used in this country for finding out what people eat. Each has its merits; each its disadvantages.

**Food habit inquiries.** Knowledge of the ideas or concepts people have about foods and their use, and the influence of culture on food consumption habits are necessary to an understanding of how to formulate educational programs regarding food. Studies which tend to be concerned with *what* is eaten and *why*, rather than *how much*, involve techniques devised by psychologists, anthropologists, and sociologists. These techniques are not discussed in this article. The reader is referred to Bulletin 111 of the National Research Council, a Committee report entitled "Manual for the Study of Food Habits."

As part of a food habit inquiry, a prepared form often is used on which are recorded menus, or the number of servings eaten of all foods or of specified types of food as, for example, the "Basic Seven." Size of servings is sometimes asked. The period may cover the last day or two, or records may be kept for as long as a week; additional questions may be asked relative to usual eating practices. This method is often used with groups—classes of school children or clubs of homemakers—each member filling in an individual questionnaire.

Such food habit inquiries often are employed as quick checks to indicate probable shortcomings in the diet when precise quantitative data are not needed or cannot be obtained. They answer the question—"Does the subject take none or some of this important food?" Depending on the questionnaire, they may tell also—"How often?" But they usually fail to give—"How much?" An example of the use of this method to indicate the results of classroom nutrition teaching is a before-and-after study in a rural county in Minnesota (U. S. Office of Education, Nutrition Education Series, Pamphlet No. 5, 1944).

From the viewpoint of the nutrition specialist, the limitations of the qualitative data which result from food habit inquiries are obvious. Even when the number of servings is obtained, the data are difficult to evaluate because of the wide

variation among families and public eating places in size of servings; an added problem is differences in choice of ingredients and their proportions in mixed dishes. Moreover, the quantity of food left uneaten on plates is rarely, if ever, taken into consideration.

**Nutrient intake of individuals.** At the other extreme from the methods employed in a survey of food habits are those used in quantitative studies of food consumption connected with nutrition investigations. The latter are characterized by being more concerned with the quantity of nutrients rather than the quantity of commodities consumed. The techniques involved are those of analytical chemistry. Each food as eaten may be analyzed for its nutritive content and from such data plus facts on quantities (by weight) actually consumed, the nutritive value of total intake of food may be computed. Or, a composite representing a duplicate or an aliquot of a meal or series of meals may be blended, and analyzed *in toto*.

The laboratory assay method is especially useful under controlled situations such as can be maintained in determining dietary requirements of individuals, or in analyzing diets served in institutions. It has been used, however, under less controlled conditions; for example, Winters and Leslie followed these procedures in studies of the diet of women in low-income and moderate-income groups in Texas (J. Nutrition 26: 443, 1943 and 27: 185, 1944).

A food record method also may be used to study the nutrient consumption of the individual. For each subject the weight (in grams) of each food served at meals and between meals and the weight of any food left uneaten is recorded; from these data the total weight of each food eaten over a period of a day or week is obtained, and the nutritive value is calculated from tables of average food composition. For mixed food products, the weight of the ingredients in the recipe and the weight of the resulting food after cooking are determined in order to calculate from tables of average composition the nutritive value of each food combination.

McHenry, among others, has used the method of recording quantities of food consumed coupled with calculation of nutritive value in his study of family food consumption in Toronto. In his studies each of the members of the household was included as separate subjects, and a family food record study accompanied the individual.

reecord studies. (Canadian Pub. Health J. 30: No. 1, 4, Jan. 1939.) This method provided facts as to how the food supply of the family was shared by its members, as well as data on food consumption of persons in various age, sex, and activity categories. Greater reliability probably can be expected from studies containing these two features—inclusion of all members of the household and a simultaneous family study. They provide cross checks if consumption for any member seems questionable.

Determination of the nutritive content of a subject's food by laboratory assay eliminates some of the assumptions inherent in data for which nutritive values are calculated from tables of average composition and from the weights of the ingredients involved. It lessens error due to losses in preparation, especially if the analysis can be done promptly on cooked food.

Studies of the quantities of food customarily eaten by individuals at a family table are subject to certain types of errors. There is a great temptation for the subject to modify his usual eating patterns. For example, he may eat all of the food served to save the trouble of weighing uneaten food; and, for the same reason, he may forego a second or third helping. The amount of food prepared may also bias the quantity eaten, since there must always be a sample for analysis. In addition, the family often is tempted to impress the investigator with its high (or low) standard for food. For these reasons, the food pattern followed may be different during the period of a study from that at other times.

*Quantities of food commodities available for family consumption: Family food accounts.* Food accounts or diaries, simple running reports of the food bought, produced or eaten, can throw much light on food consumption patterns. This method was used by the U. S. Bureau of the Census in 1943-44 to gather data on food purchases from a random sample of the population. Its purpose was to assist the Office of Price Administration in making decisions on point values and the distribution of civilian food in relatively short supply. Such records also are kept by many farm families, accounting for income received in the form of home-produced food, as well as disbursement of money income for purchased food.

While such data can be collected inexpensively, because little supervision generally is involved, the time required to summarize the data from each family and prepare it for tabulation prior to analysis offsets savings in collection. If kept over a long enough period of time, inventories of food on hand at the beginning and end of the study presumably balance. But the method has other disadvantages which are likely to impair the statistical value of the findings. Participation is limited

to families that include a member able and willing to keep accounts. This eliminates some foreign-born families and those with little schooling or low mental capacity. Because the period covered tends to be long and stimulation from the supervising agent generally infrequent, there are always an appreciable number of families that lose interest in an account-keeping project and discontinue their participation. Moreover, for the same reasons the account keeper is likely to neglect to enter purchases and to grow more careless in this respect as the study progresses.

*Family food records with inventories.* These family food records consist of a weighed inventory of the food on hand at both the beginning and end of the period of study plus a daily account of the weight of other foods brought into the home during the time covered, usually a week at a time. This period is as short as will cover the day-to-day actual pattern of eating in this country; it is as long as is generally feasible if cooperation is to be maintained. A supervisor helps the homemaker with both inventories and makes visits to the home almost daily during the week to supervise entries on the record.

Schedules usually provide for a record of the sex, age, and physical activities of the persons who who ate from home food supplies during the period of study and the number of such meals eaten by each. Usually only the food consumed at home is included as it is difficult for the homemaker to supply detailed information about food eaten outside the home by other members of the household.

This method was used exclusively in the study of diets of wage-earning families made in 1934-36 (U. S. Dept. of Agriculture, Circular 507) and as one of the methods employed in the 1935-36 Study of Consumer Purchases (U.S. Dept. of Agriculture, Misc. Publ. 405 and 452).

*Family food list (estimates).* Family food lists are verbal reports on the food consumed at home during a specified period. The reporting is done by the person most responsible for the purchase and preparation of the family's food, usually the homemaker, to a field agent. The data are recorded on a prepared schedule containing a detailed list of food items that serves as a reminder for the respondent. Family food lists differ from family food records described above in that by the list method consumption is reported from memory in terms of weights or common household measures. Like family food records, food lists should include information on the persons served from home food supplies and the number of meals served. Unlike the food record, all the data are obtained in a single interview, and most frequently concern a period immediately prior to the visit of the field agent.

A respondent can discharge her obligations as a participant in a food estimate survey quickly and easily. Even in a difficult situation the agent should be able to complete the one interview necessary in less than one hour. The rate of participation, therefore, is high, making it a suitable method for getting food consumption data from a representative cross section of a population group. The accuracy of food data collected by the es-

family food record and food list (estimate) have been used to provide dietary information. They can show on a national or regional basis the effect of different circumstances of time and place, of size of family, and of economic situation on levels of food consumption.

Large-scale dietary surveys make possible any number of special analyses. They can show, for example, how much families at different income

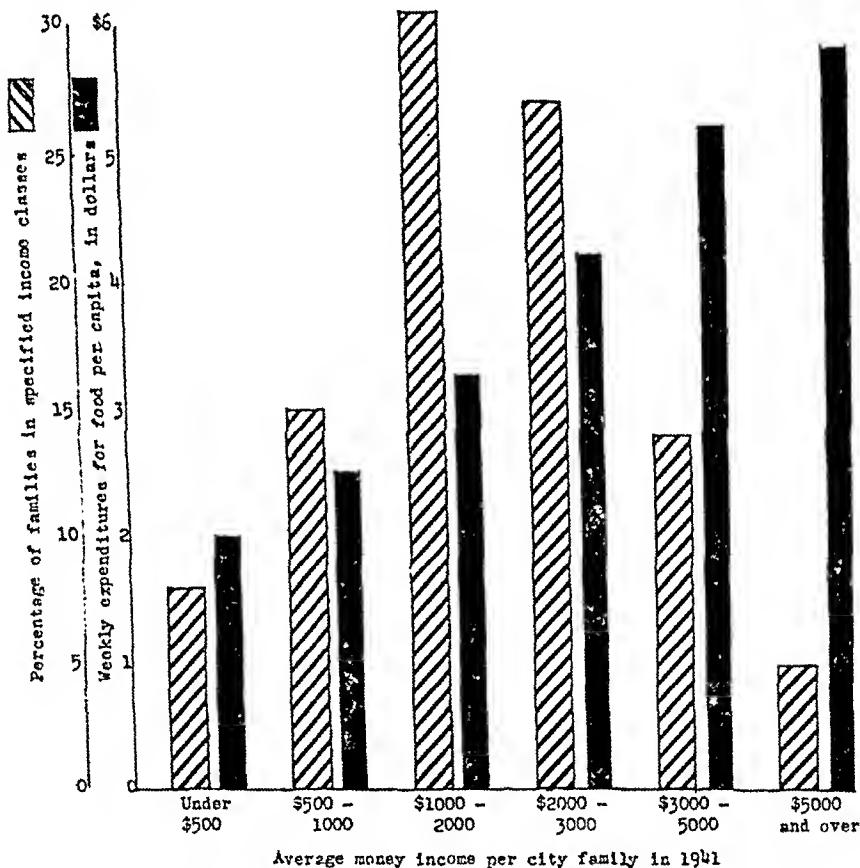


Fig. 1. Distribution of families by money income level and average expenditures for food per person per week, city families, 1941.

timate method depends largely on the memory of respondents. It is expected that errors of overestimation and underestimation by respondents in the group compensate each other in the averages in which the findings are given. It is a useful method, therefore, when time and money are short. It can be satisfactory when averages for groups of families rather than facts regarding individual families will serve the purpose of the study. This method was used in a study made in 1942 of family food consumption in this country (U. S. Dept. Agriculture, Misc. Publ. 550).

*Uses of large-scale dietary studies.* Both the

MONEY INCOME CLASS	CITY FAMILIES IN CLASS		AVERAGE EXPENDITURES FOR FOOD PER PERSON PER WEEK
	per cent	dollars	
Under \$500	8	1.98	
\$500-\$999	15	2.46	
\$1000-\$1499	15	3.28	
\$1500-\$1999	16	3.44	
\$2000-\$2499	15	4.18	
\$2500-\$2999	12	4.28	
\$3000-\$4999	14	5.20	
\$5000 and over	5	5.80	

levels spend for food. As may be seen from the tabulation on p. 255 and figure 1, over half of our urban families had money incomes of less than

mines how much will be spent for food. In 1941, urban families with money incomes of less than \$260 per person per year spent more than half of

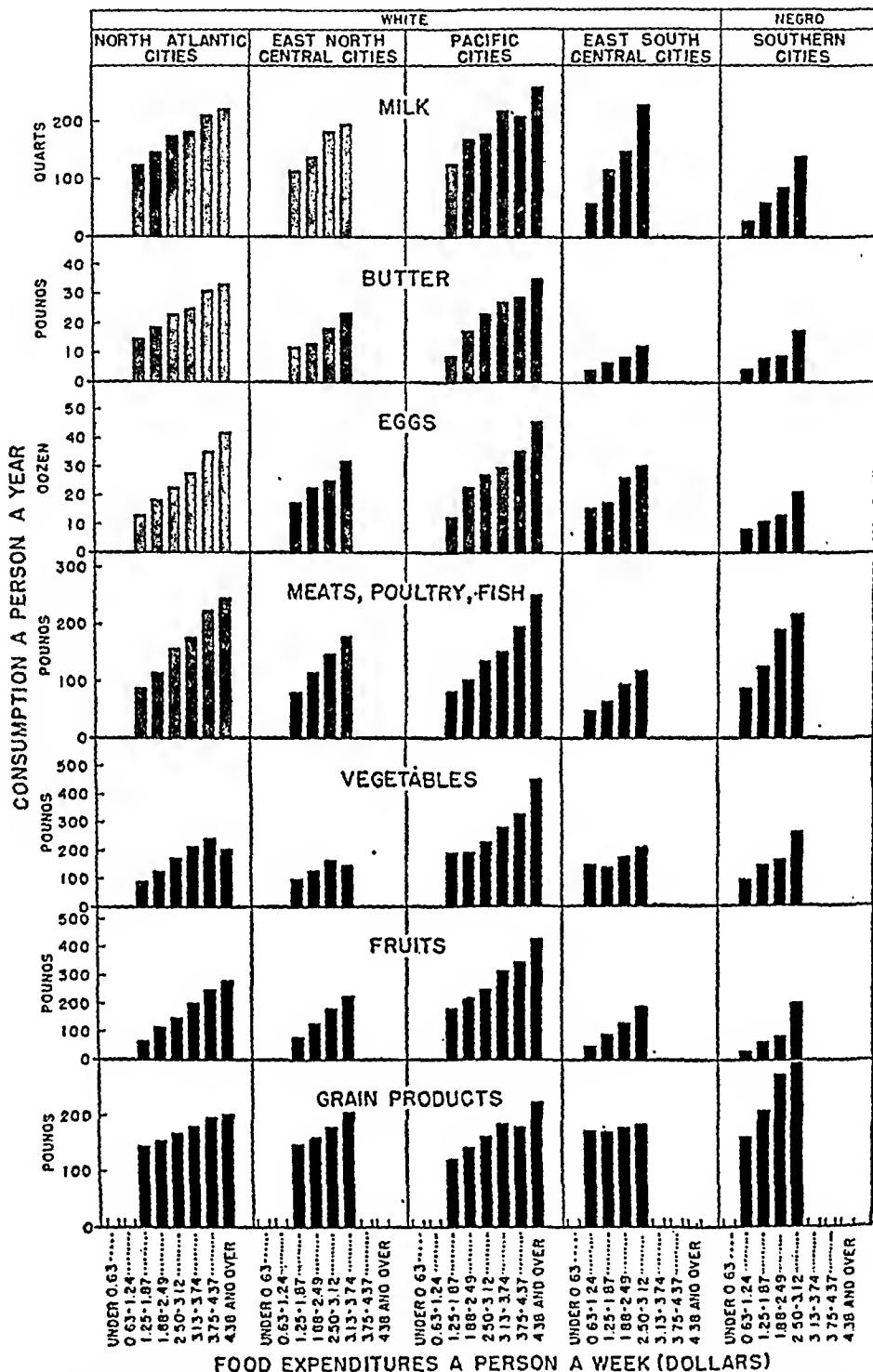


Fig. 2. Average consumption per person per year of specified articles or groups of foods, by families in different regions spending different amounts for food, 1936.

\$2000 a year in 1941, and average food expenditures of less than 50¢ a person a day.

Size of family as well as size of income deter-

their money for food. Only when the year's income exceeded \$410 per family member did the proportion spent for food fall below 40 per cent.

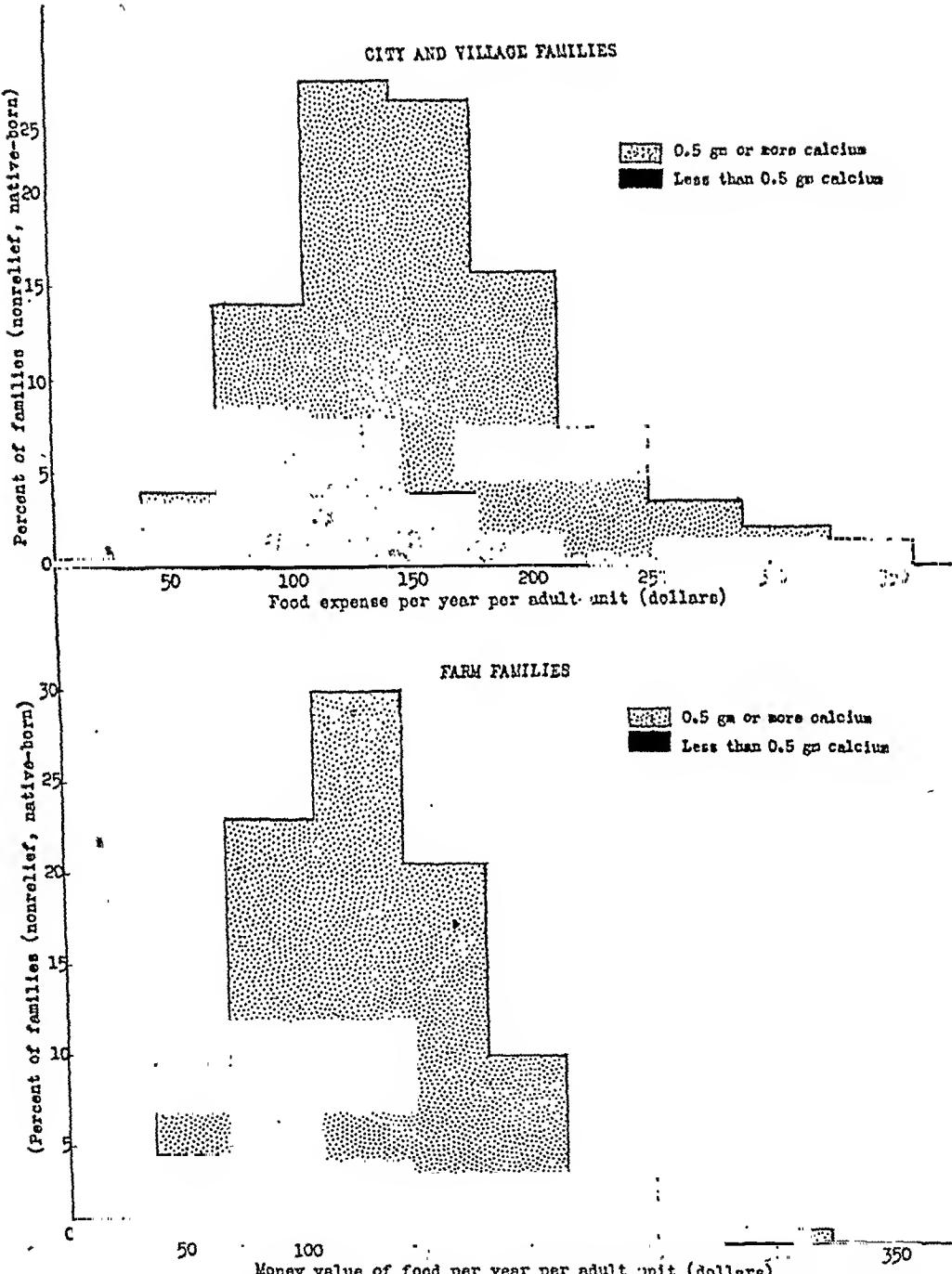


Fig. 3. Distribution of families by money value of food, and proportion with diets furnishing more and less than 0.5 gram calcium per adult unit per day, 1936.

This type of information gives the economic setting against which to interpret data on dietary patterns and the nutritive content of diets. Interest in trends in food consumption and nutritive

value of diets with rising incomes should not obscure the position of the bulk of the Nation's families with respect to income and money for food.

Nation-wide dietary surveys yield information

on the kinds and quantities of foods consumed in the United States as a whole and by different groups—different regions, different size families and different income groups. The report of the spring 1942 survey (Family Food Consumption in the United States U. S. Dept. Agr. Misc. Publ. 550) for example, contains information on the consumption in the spring months of some 170 separate items of food as well as for several groups of food. Such data have many uses. When the enrichment of bread and flour was under consideration, for instance, it was possible to estimate the dietary improvement for various population groups that would result from different levels of enrichment. Again when the rationing program was being developed, the Office of Price Administration studied very carefully the consumption of various foods by different income and regional groups.

Food consumption data furnish a basis for estimating the effective demand for food with shifts in income. This is perhaps one of the most important uses in connection with planning for food production and distribution. The Department of Agriculture and others concerned with such problems are tremendously interested in the probable demand for agricultural products under various assumptions as to income. Business men, as well as farmers, are interested in the market outlook for their food products. Any food distribution plan for low-income families needs to take into account food consumption patterns and the additional kinds and amounts of food such families can be expected to use if they are given additional purchasing power.

Such studies show that as consumers have more income and more money for the food of each person, consumption is increased of fruits, especially tomatoes and citrus fruit, of succulent vegetables, especially the leafy, green and yellow kinds, and of milk, eggs, meats, poultry, and fish. On the other hand, consumption of such food groups as potatoes and sweetpotatoes, mature beans and peas, flour and cereals, sugars and fats, usually increase at a much slower rate, if at all. This varies from one population group to another, as shown in figure 2.

An important part of any analysis of food consumption data is the translation of commodities into terms of nutrients. Average values for groups of families (such as can be obtained either from family food records or from family estimates of consumption) are useful for studying trends from time to time or from one income group to another. They show the effects of such factors as income, family size, region and type of community on possible nutritional levels.

Family food records with inventories of food brought into the kitchen are accurate enough to justify the calculation of the nutrients available in the food supply of each family. From these data one can determine the percentage of all families studied or of those in different population groups whose diets during the period of study furnished specified quantities of various nutrients. Figure 3 shows, for example, the proportion of families in two groups whose food in 1936 provided more or less than a half gram of calcium per adult unit per day. From a study of the distribution of families by level of nutritive value of their available food supply, we also have estimated that about one-fourth of the families in the United States had diets in 1936 that met the National Research Council's recommendations for riboflavin; and about half had diets that met the allowances for calcium, thiamine and ascorbic acid. In the spring of 1942 somewhat fewer than half of the families had diets that met or exceeded the recommended allowances for riboflavin, whereas about two-thirds met the allowances for calcium, and the same proportion or more, the allowances for thiamine and ascorbic acid.

• (By "diets" in the foregoing paragraph is meant the food brought into the kitchen for family consumption. Since in the analysis quoted above no deductions were made for the invisible losses in food preparation, or for waste other than average refuse, the picture drawn is the most optimistic one possible. The trends probably are correct; the exact proportions suggest more generous provision of the more heat-labile and water soluble nutrients than is the case.)

## DEVELOPMENTS IN PUBLIC HEALTH NUTRITION APPRAISAL

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All dietary surveys have indicated that a large part of the American people eat diets that are inadequate when compared with recommended allowances. Surveys conducted in different parts of the country have indicated that malnutrition

is a serious problem in both rural and urban populations; it is found in children and adults; although it is more prevalent in low economic groups, it is found in all economic levels and in all sections of the country. The percentage of inadequate diets

varies from one group to another. Dietary inadequacy is more serious in some sections than in others, but the evidence we now have indicates that it is a national problem.

On the other hand, we have very inadequate clinical data on the kind, severity, and prevalence of deficiency diseases in this country. It is true that a few studies of nutritional status have been made by various groups working in different parts of the country.<sup>1</sup> However, these studies have been too limited in scope to give us an adequate picture of the problem as it affects the country as a whole—or even the states in which work has been done. It is impossible to attack the problem of prevention of deficiency diseases satisfactorily without knowing the kinds of deficiencies in the area concerned, their prevalence, and the people affected by them.

Nutrition education and schemes for making food available to low income groups are very valuable as preventive measures, but they do not furnish those extra measures that are necessary to cure existing deficiencies quickly, nor do they give special attention to various groups of people seriously needing help. It should be a health department function to find, diagnose, and determine the prevalence of deficiency diseases. Knowledge of this type is a fundamental necessity for an adequate control program.

There are difficulties to be overcome in making nutrition appraisals on a public health scale. There are differences of opinion about interpretation of various lesions, and often there is failure to recognize the importance of very mild symptoms. The need for adequate study is very great, and further development should be rapid and extensive.

For many years the United States Public Health Service has conducted research on the deficiency diseases; this work was started because of the seriousness of the pellagra problem in this country and the lack of knowledge about it. Now our knowledge of nutrition has reached a point where adequate treatment and prevention are possible for all known deficiency diseases.

The National Nutrition Conference held in May 1941,<sup>2</sup> recommended that diagnostic service in deficiency diseases be made available to health departments and physicians as soon as methods of proven value are developed and that local and state health departments take a greater interest in nutrition.

<sup>1</sup> Inadequate diets and nutritional deficiencies in the United States: their prevalence and significance. Bulletin 109. National Research Council.

<sup>2</sup> Proceedings—National Nutrition Conference for Defense, 1941, Government Printing Office—110.

In carrying out this recommendation, an important part of the work of the nutrition division of the Office of Defense Health and Welfare Services dealt with health officers and physicians. The first effort was to encourage cooperation among health officers, nutritionists, and other Health Department staff members in making the best use of our knowledge and resources in the prevention of deficiency disease during the emergency period just preceding the war.

In June 1942, an officer of the United States Public Health Service was assigned to the Nutrition Division of the Office of Defense Health and Welfare Services to work as nutrition consultant for public health officials and medical and dental practitioners. The objective was to stimulate further development of the public health and medical aspects of the national nutrition program.

Throughout the development of this work, meetings of public health, medical, and dental organizations have been attended by the medical officer. Nutrition as it relates to health has been discussed with individuals and groups attending these professional meetings. Panel discussions of the public health aspects of nutrition have been held, and talks have been made at national, state, and local meetings of public health, medical, and dental groups. On invitation, the medical officer helps State and local health departments plan further development of their public health nutrition programs. As a further service to State and local health departments, carefully selected material dealing with the public health aspects of nutrition has been made available to health departments.

In this work the handicap of trying to prevent deficiency diseases without adequate knowledge of their prevalence or location has been fully recognized. Soon after the Nutrition Division was transferred to the Nutrition Programs Branch of War Food Administration, an experimental clinic was held for the purpose of demonstrating the signs and symptoms of deficiency diseases, for discussion of their prevalence, and to stimulate interest in their recognition, treatment, and prevention. This was followed by four regional clinics. They stimulated so much interest that numerous requests for similar demonstrations were received from state health officers and other interested state officials. Demand for this service resulted in the development of a clinic procedure designed to assist health officers in discovering the best method of activity and organization to provide adequate public health nutrition services.

Nutrition clinic demonstrations have been organized by State and local health departments at the request of State nutrition committees. The Nutrition Programs Branch has assisted by providing the services of the United States Public Health Service officer assigned to the Branch. He

helps local health officers select patients and conducts, or assists in conducting, the clinics.

The greater part of the work connected with the clinics is done before the actual demonstrations. Clinic demonstrations are usually held in a central place in the State; representatives of local nutrition committees and other organized groups from various parts of the State attend. In states where several clinics have been held, the State has been divided into sections and clinics planned so that representative groups from the surrounding areas could attend with a minimum of travel.

An attempt is made to keep the meetings small and to make them informal and effective. In most cases, tickets are provided by the nutrition committee. This committee and the health department distribute the tickets to people who represent agencies and groups working on various aspects of the nutrition problem. Each county or city in the area served by a clinic is usually represented by people from several official and voluntary agencies.

In places where there is no local health department, plans for organizing and conducting nutrition clinic demonstrations have sometimes been worked out with other local medical organizations or groups, such as medical societies, medical schools, and hospital clinics.

Preparation for nutrition clinic demonstrations includes a limited preliminary study of school children of the area where the conference is to be held. The problem is tackled from several approaches:

1. Limited, easily appraised diet records are obtained from groups of school children in order to learn their diet pattern.
2. Children who have submitted diet records are inspected for a few of the specific signs that have been associated with nutritional deficiency diseases. These are recorded on a form; positive findings are designated in pluses—for example:

questionable.....	.....	1+
mild, but definite.....	....	2+
moderate.....	.....	3+
marked.....	.....	4+

3. When time and facilities permit, children who show physical signs suggesting specific deficiencies are tested therapeutically with the nutrient the lack of which is thought to cause the condition.

4. Where possible, laboratory work is done—including blood hemoglobin by a reliable method, vitamin C levels in plasma, and X-rays of suspected cases of rickets.

Final work-up of the nutrition clinic demonstration includes a limited appraisal of groups of school children in the area by the United States Public Health Service medical officer. He also

inspects younger children and adult patients who have been tentatively selected by the local health officer, local physicians, and dentists.

At clinics held in various parts of the country, the following signs, which often indicate nutritional deficiencies, have been exhibited:

1. Signs suggesting anemia (pale mucous membranes, etc.)
2. Signs often associated with rickets (active or healed)
  - a. Parietal bossing
  - b. Craniotabes
  - c. Flaring ribs
  - d. Harrison's groove
  - e. Rachitic rosary
  - f. Pigeon breast
  - g. Funnel breast
  - h. Pot-belly
  - i. Bowlegs or knock-knees, etc.
3. Generally poor development (especially in children)
  - a. Marked underweight or overweight
  - b. Flabby muscles
  - c. Poor posture
4. Nutritional edema
5. Signs of infantile scurvy
6. Rough skin (folliculosis)-goose-pimple-like lesions that are sometimes associated with vitamin A deficiency
7. Dermatitis of pellagra
8. Dry rough hair
9. Cracks, sores, or scars at corners of eyes
10. "Granulated" lids
11. Crusty eyelids
12. Inflamed lid margins (blepharitis)
13. Eyes oversensitive to light (photophobia)
14. Vascularization of cornea
15. Burning, itching, or blood-shot eyes
16. Thickening of sclerae
17. Poor eyesight due to nutritional deficiencies
18. Chronically peeling lips (cheilosis)
19. Cracks, sores, or scars at corners of mouth (angular stomatitis)
20. Swollen, spongy, bleeding gums (gingivitis)
21. Slick tongue
22. Purplish tongue
23. Beefy red tongue (glossitis)
24. Mottled enamel
25. Dental caries
26. Goiter (simple)

In some clinics infants with scurvy and patients with pellagra have been shown. Their cases have been discussed and pellagra patients have been questioned about the kind and onset of their symptoms and about their previous and present diets. Mothers of infants with scurvy or rickets have been similarly questioned about the diets of their babies.

The following procedures are among those that

have proven successful in presenting nutrition clinic demonstrations.

1. The local nutrition committee chairman, or a person designated by the chairman, presides at the meeting. This person gives a brief statement of the objectives of the meeting.

2. All discussion is in language that laymen, especially the patients, can understand.

3. The physician who conducts the clinic gives a brief discussion. He outlines the important points concerning the purpose of the demonstration.

4. A representative of the State health department discusses the importance of nutrition in relation to health problems of the State or the local community.

5. A representative of a State agricultural agency points out the relationship between soils, food production, and human nutrition. Illustration with slides and charts often proves very effective.

6. A school official or teacher discusses the nutrition problems of school children.

#### *7. Presentation of Patients*

Arrangements are made for getting patients to the clinic. When a small child is to be presented an adult responsible for the care of the child is present. Good rapport is established with the patients. Each patient is given a complete explanation of the purpose of the meeting he is to attend and the part he is to play in it.

Even though the clinic is held primarily for the benefit of the nutrition committee and guests, adult patients and older children are seated as part of the audience. They not only benefit from the whole discussion, but are more at ease when they actually participate in the meeting. At no time are they made to feel that they are on exhibition.

The patient is sometimes presented as a "case". The history, principally dietary, is sometimes given by the doctor or nurse with the patient taking no part in the discussion. Sometimes the patient participates in the discussion by answering questions or by giving his own history. The audience is encouraged to ask questions at any time during the demonstration. This helps to keep the discussion centered on local problems and to provide information needed by workers who are participating in the local nutrition program.

In discussing each case, the shortcomings of the diet are emphasized and specific recommendations for improvement are offered. These recommendations are suggestions for dietary changes, or additions to the diet. It is always suggested that the patient consult his own physician or dentist—if he has one. When it seems advisable, it is suggested that patients who have no family physician go to a clinic for guidance.

Follow-up procedures, which can be carried out

by local public health workers, are planned. A brief outline of the follow-up plan is valuable to the audience and helps show the patient the importance of putting the recommendations to work.

Slides are shown of deficiency diseases found in the section where the clinic is held; they are discussed by the physician who presents the clinic. A few slides showing well-developed and well nourished children, are used to emphasize the importance of good nutrition to normal development. Sometimes several well-developed and well nourished children are shown; however, this is done at an earlier or later meeting to avoid making comparisons that might embarrass the malnourished children or their parents.

In order to give workers in the National Nutrition Program a better understanding of good and poor nutrition, the following points are emphasized at nutrition clinic demonstrations:

1. That most of the malnutrition in this country is found in mild or moderate forms.
2. That malnutrition is a *group of diseases* to which many factors contribute, and that understanding the problem depends on appreciation of its various aspects.
3. That signs and symptoms of malnutrition may be caused by organic or functional disturbances or disease conditions; therefore, malnutrition *in the individual* should be recognized as a medical problem that should be diagnosed and treated by a physician.
4. That the solution of *community nutrition problems* depends on appreciation of the various aspects of these problems by all individuals and agencies working in the field of nutrition—and on their coordinated efforts to work out solutions.
5. That most malnutrition can be prevented by establishing and maintaining good food habits, together with wise production and utilization of food.

To date 66 clinic demonstrations have been held in 24 states in all sections of the country. In all areas, we have found a wealth of evidence suggesting deficiency disease. The evidence also suggests that deficiency disease is widespread in school children in this country and that there is serious need for more adequate health department service in the field of nutrition. Health officers have recognized this fact. We have received numerous requests from them for assistance in appraising the nutritional status of various groups in the populations they serve. However, we have not had the staff or funds needed to provide the services that health officers have requested.

The clinic demonstration technique has been an experiment in a field of public health that has hitherto been unexplored in this country. The

clinics have been conducted with a minimum of personnel and very restricted funds. These limitations have made it impossible for us to study conditions in enough detail, and for long enough periods of time to make positive diagnoses, to recommend adequate control measures, or to observe the results of such measures. The clinic demonstrations are now being expanded to include adequate laboratory work, thorough diet histories, therapeutic tests, ease follow-up, nutrition education, and the institution of preventive measures.

Funds have been made available to the United States Public Health Service to set up mobile units to carry on an expanded and intensified program of nutrition appraisal in cooperation with State and local health departments. Each mobile unit will be staffed by a medical officer, a nutritionist, a biochemist, and a nurse.

Help will be given to State health departments in establishing their nutrition appraisal programs. The staff of the mobile unit will work with State and local health departments on appraisal of the nutritional status of population groups within the State. Their job will be to find, diagnose, and determine the prevalence of deficiency diseases and to recommend measures for prevention and control.

We anticipate that the following general approaches will be used: Physical examinations, Laboratory examinations, Histories, Diet records, Therapeutic tests, Nutrition Education. An important part of the staff's work will be to appraise and analyze the procedures used and to attempt to streamline and simplify the process of nutrition appraisal of groups.

Another essential part of the work will be to help the State health department work out plans for taking over the nutrition appraisal program after the mobile unit leaves. We anticipate that the health department will assign some of its staff to work with the mobile unit staff. These health department staff members will gradually take over the nutrition appraisal program within the State. They will use the methods and techniques that have been developed. We hope that eventually they will be able to offer similar services to their local health departments.

As State and local health departments collect data about the kinds, prevalence, severity, and locale of nutritional deficiencies within the State they will be able to make this information available to other State and local agencies working in the field of nutrition. Thus the county health officer will be able to tell the county school superintendent how much malnutrition exists in the school children of the county, which schools are most seriously involved, and the specific deficiencies found. He will also be able to recommend measures for prevention and control. Likewise,

he will be in position to answer county agricultural workers' questions about nutritional deficiencies found in various sections of the county. Armed with this information, educational and agricultural agencies can concentrate their work on a known problem, can work far more effectively on it, and can measure the results of their nutrition work more adequately.

The problem of food and nutrition is our greatest and most complex problem in preventive medicine. Health officers are recognizing the fact that the nutrition problem presents a whole new sphere of health department responsibility. They are continually asking for help in this field.

In March 1943, the rôle of the health department in the national nutrition program was discussed at the annual meeting of the State and Territorial Health Officers Association.<sup>3</sup> At that time the lines were indicated along which State health departments can work to develop nutrition programs that are in keeping with sound principles of public health. Among the suggestions offered for State health departments, were the following:

1. Collect information and do appraisals on the incidence and types of deficiency diseases and on food habits in geographical areas and population groups.
2. Offer assistance to other agencies in the diagnosis of nutritional deficiencies.
3. Prepare and distribute simple attractive material on State nutrition problems.
4. Cooperate with other agencies dealing with different aspects of the nutrition problem.
5. Take an active part in the work of the State Nutrition Committee.
6. Offer information, consultation, guidance, and encouragement to local health departments in developing local nutrition appraisal programs.
7. Promote staff education in nutrition.

Recommendations to local health departments adapted these suggestions to local problems and facilities. For example, some specific suggestions for a school health program were.

1. Cooperate with other groups in improving school lunches.
2. Watch for signs of nutritional deficiencies when doing physical examinations of school children.
3. When practical, sponsor demonstrations with school children showing results of improved nutrition.
4. Sponsor limited surveys of the nutritional status of school children.

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<sup>3</sup> Sebrell, W. H. and W. Wilkins. The Rôle of the Health Department in the National Nutrition Program. *Public Health Reports* 58: No. 21, May 21, 1943, 803-813.

We still believe that State and local health departments can develop more effective nutrition services by working along these lines. They can choose from the above suggestions the things they can do now and can gradually expand their programs as public health nutrition work develops.

Nutrition must take its place in the health department along with sanitation and communicable disease control as a major function in maintaining

health. This can be done when the health department can determine the kind, extent, and location of the problem. Adequate appraisal of nutritional status is just as essential in prevention and control of malnutrition as a tuberculosis survey is in the control of tuberculosis. We believe that nutrition appraisal will provide the fundamental information needed to develop more nearly adequate nutrition programs in the community.

## NUTRITION STUDIES IN THE NEW ORLEANS AREA

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Nutritional deficiency has been an important problem in Louisiana for many years. While the incidence of severe deficiency disease, such as pellagra and beriberi, has decreased markedly in the past decade, mild deficiency syndromes are still common and the dietary habits of a significant proportion of the population are far from ideal.

Three dietary surveys have been conducted in various parts of Louisiana in the past few years. In each survey the methods of collecting and analyzing data were similar. A record of all food eaten for a one week period was kept by the individual or family being studied. Diets were evaluated by means of a score card based upon the recommendations of the Food and Nutrition Board of the National Research Council. Protective foods were classified in ten groups each of which was graded good, fair or poor depending upon the number of servings during a one week period (table I). The total diet was evaluated by giving each food classed as good a score of three points, fair two points, and poor one point. A diet in which the total score was 25 or more was found by calculation to fulfill the recommended allowances of the National Research Council in all respects and was designated good. A diet with a score of less than 15 was found to be distinctly deficient in one or more essential nutrients and was classed as poor. A fair diet, with a point value of 15 to 24 was borderline furnishing in many instances an insufficient amount of some of the necessary food factors.

The first dietary survey conducted in 1939-1940 by Grigsby, McBryde and Davis (1), involved 1082 Farm Security Administration families. The second survey, carried out in 1942 by Bryson, Tucker and Davis (2) included 780 Home Demonstration Club members' families in 27 parishes in Louisiana. The third study, reported in 1943 by Coco, Moore, Goldsmith, Lucas and Davis (3) dealt with the adequacy of diets of grade and high school students. A total of 5,776 records were

collected in New Orleans, 377 in Crowley High School and 545 in grade and high schools in other areas in the state. The findings in these three surveys are given in tables II and III. Only a small number of persons in each of the groups studied were found to be receiving a diet which measured up to the standards recommended by the National Research Council (table II). The poorest diets in each of the surveys were found in the negro groups where 59 to 75% were classed as poor and 0.0 to 3.3% good. The best diets were obtained by the families of Home Demonstration Club members, 41% being classed as good, 51% fair, and only 8% poor. These findings may be compared with those of the 1939-40 survey of Farm Security Administration families in which only 1% were good, 69% fair, and 30% poor. The apparent improvement in diet from 1940 to 1942 may be due to a number of factors such as differences in the groups studied, changes in economic status in these years and the influence of the nutrition educational program. The adequacy of diets of the families of Home Demonstration Club members varied in different agricultural areas in the state being slightly better in the rice area than elsewhere and poorest in the sugar cane area, where only 8% of diets were rated good while 27% were poor. Data obtained in this survey indicated that families who practiced diversified farming had a larger variety of protective foods than families who followed a one crop system. Home production and conservation of foods and the ownership of farm animals tended to increase the adequacy of diets. The size of the family did not appear to influence the findings. There was a tendency for diets to improve as income increased.

In table III the frequency with which each of the protective food groups appeared in the diets is indicated. Whole grain cereals were used in recommended quantities less often than any other food. The consumption of fruits, vegetables and butter was uniformly low except among the families of Home Demonstration Club members. Eggs and

milk were used in substandard amounts in many instances. Meat and meat substitutes fulfilled recommended allowances more satisfactorily than any other food group. Seven of the protective foods were scored "good" in less than 50% of the diets. Among negroes even lower figures were obtained.

From these data it is impossible to state specifically which essential nutrients were most often ingested in insufficient amounts. However, the low consumption of whole grain cereals suggests an inadequate supply of thiamine. Diets which were low in fruits, vegetables, milk and butter

TABLE I  
*A score card for determining the adequacy of diets*

	SERVINGS PER WEEK		
	Good	Fair	Poor
Milk.....	14 or more	8-13	7 or less
Butter.....	14 or more	8-13	7 or less
Eggs.....	5 or more	3- 4	2 or less
Lean meat or substitute*.....	7 or more	4- 8	3 or less
Vegetables			
Green, leafy, or yellow.....	7 or more	4- 6	3 or less
Others.....	7 or more	4- 6	3 or less
Potatoes.....	7 or more	4- 6	3 or less
Whole grain cereals.....	10 or more	5- 9	4 or less
Fruits			
Citrus fruits or tomatoes or...	7 or more	4- 6	3 or less
Raw vegetables†	7 or more	4- 6	3 or less
Other fruits.....	7 or more	4- 6	5 or less

\* Lean meat as such must appear at least four times a week. Meat substitutes include cheese, dried peas or beans and soybeans.

† The only raw vegetables which may be included in this group are cabbage, green peppers and radishes.

as well as in cereals, appear to be deficient in minerals, all members of the vitamin B complex, vitamin C and vitamin A.

In 1942 the Louisiana State Board of Health (4) conducted a survey in 17 representative parishes throughout the state in the course of which 779 children were given a general physical examination to determine nutritional and general health status. Of this group, 545 also participated in the dietary survey discussed above (see tables II and III, Other Schools). Of the 779 children examined 44% were judged as definitely undernourished while 13.4% of the white and 24.4%

of the negro children were considered to be in poor or very poor nutritional condition. It was noted that 86% of the children had dental defects in need of correction, 33% poor posture, 24% some type of intestinal parasite and 11% anemia. These findings are corroborative of those obtained in dietary studies in the same children in which 40% of the white and 75% of the negro group were found to be receiving poor diets.

In 1943 Goldsmith and Bryan (5) examined 45 negro children in a school in Donaldsonville, La. as part of a special nutrition project. A check off type of card was used for recording the information desired. The symptoms and signs which might be ascribed to nutritional deficiency in these children are given in table IV. The findings suggested

TABLE II  
*Adequacy of diets in Louisiana as judged by recent surveys*

GROUP STUDIED	EVALUATION OF DIET (%)		
	Good	Fair	Poor
Farm Security Administration families, white..	1.2	69.3	29.5
Farm Security Administration families, negro..	0.0	32.2	67.8
Home Demonstration Club Members families..	41.0	51.0	8.0
Grade and High School students, New Orleans, white.....	11.2	59.6	29.2
Grade and High School students, New Orleans, negro.....	3.3	38.1	58.6
High School Students, Crowley, white.....	14.5	73.1	12.4
Other Schools in State, white.....	9.0	54.1	36.9
Other Schools in State, negro.....	0.3	24.5	75.2

vitamin A deficiency in 26 children, deficiency of the B group of vitamins in 31, ascorbic acid deficiency in 4 and evidence of old rickets in 20. Similar findings were commonly observed during recent visits to schools in various parts of Louisiana.

In November 1944, Wilkins and Moore (6) examined 643 school children in the Baton Rouge and Shreveport areas for certain signs which occur frequently in association with nutritional deficiency. They found that 33% of the children had crusted cyclids, 31% folliculosis of the arms or thighs, 63% changes in the gums (hyperemia, sponginess or bleeding), and 92% dental defects. In addition, 46% had scars at the corners of the

mouth, 11% angular stomatitis, 89% flaring ribs, 66% some degree of bossing of the skull and 61% were somewhat knock-kneed.

respective illnesses may have increased the requirement, decreased absorption or interfered with the utilization of nutrients. The patients were

TABLE III  
*Frequency of protective foods or food groups in diets in Louisiana*

FOOD GROUPS	N.D.C.*	PER CENT PRESENT IN ADEQUATE AMOUNTS				
		New Orleans schools		Crowley schools	Other Schools	
		White	Negro		White	Negro
1. Meat and meat substitutes.....	81	79.9	68.4	89.4	72.9	70.7
2. Eggs.....	72	21.5	16.0	32.3	32.2	15.2
3. Milk.....	71	42.6	10.5	67.7	49.0	5.2
4. Green leafy and yellow vegetables..	66	49.1	25.1	64.1	26.3	6.7
5. Other cooked vegetables.....	59	22.7	16.2	38.5	17.3	6.9
6. Fruits and certain raw vegetables..	55	32.0	19.4	31.0	24.7	8.6
7. Citrus fruits and tomatoes.....	50	25.4	9.7	29.5	18.4	5.5
8. Butter.....	47	37.0	5.4	18.9	9.4	1.0
9. Potatoes.....	46	15.9	8.0	17.1	17.3	10.0
10. Whole grain cereals.....	14	7.9	6.7	8.3	5.1	0.3

\* Home Demonstration Club Members Families.

TABLE IV  
*Findings suggesting nutritional deficiency in 45 negro children*

SYMPOMS	NO. OF CASES	SYMPOMS	NO. OF CASES
Backwardness in school.....	15	Burning and itching eyes.....	6
Nervousness and irritability.....	12	Night blindness.....	2
Repeated colds.....	11	Failure to gain weight.....	3
Aversion to normal play.....	9	Bleeding gums.....	3
Poor appetite.....	7	Sore mouth and tongue.....	4
SIGNS		SIGNS	
Skin		Eyes	
Dryness—scaling.....	29	Conjunct. thick-pigmented.....	30
Seborrhea—face.....	27	Conjunctival injection.....	20
Follicular keratosis.....	18	Photophobia.....	12
Lack subcutaneous fat.....	6	Lacrimation.....	10
Pallor mucous membranes.....	4	Bitot's spots.....	7
Pellagraous dermatitis.....	0	Circumcorneal injection.....	5
Purpura or petechiae.....	0	Mouth	
Neuro muscular		Tongue	
Poor posture.....	7	Red hypertrophied papillae.....	36
Increased reflexes.....	6	Atrophic papillae.....	1
Calf muscle tenderness.....	1	Fissures—purple.....	1
Skeletal		Red tips and sides.....	3
Beading of ribs.....	16	Serious dental defects.....	10
Enlarged wrists.....	6	Spongy bleeding gums.....	4
Other signs of rickets.....	4	Cheilosis-angle lesions.....	0

In 1943 Goldsmith (7) examined 200 patients in the medical wards of Charity Hospital for evidence of nutritional deficiency. These individuals were representative of stress groups in that their

consecutive admissions whose ages ranged from 5 to 82. There was an equal number of white male, white female, negro male and negro female patients. The symptoms and signs suggestive of

deficiency disease in these individuals are given in table V. Findings relative to niacin and riboflavin deficiency have been reported previously and may be summarized as follows: 44 persons had definite evidence of riboflavin deficiency, 11 of niacin deficiency, and 24 of deficiency of both niacin and riboflavin. An additional 54 patients had signs which were probably the result of a deficiency of these two vitamins.

Nearly one-fourth of the persons examined had findings which suggested thiamine deficiency. The

TABLE V  
*Incidence of symptoms and signs suggestive of vitamin deficiency in 200 patients\**

SYMPTOMS	NO. OF PATIENTS
Sore mouth and tongue.....	25
Chronic diarrhea.....	17
Nervousness and irritability.....	54
Paresthesia and/or muscle and joint pains.....	72
Visual disturbances (photophobia-burning-fatigue).....	80
Night blindness.....	10
Bleeding gums and/or easy bruising.....	49
SIGNS	
Nasolabial sebaceous plugs.....	65
Cheilosis.....	34
Changes in color, texture or papillae of tongue.....	111
Pellagrous dermatitis.....	9
Thick pigmented skin over bony prominences.....	90
Follicular hyperkeratosis.....	34
Conjunctival thickening.....	72
Conjunctival injection.....	44
Vascularization of cornea.....	18
Bleeding gums and/or purpura.....	14
Calf muscle tenderness.....	57
Sensory and/or reflex changes.....	45

\*From the medical wards of Charity Hospital, New Orleans, La.

high incidence of follicular hyperkeratosis, night blindness and conjunctival thickening indicated that vitamin A deficiency was common. Bleeding gums, purpura and a history of easy bruising was considered evidence of an inadequate supply of ascorbic acid in a number of these patients. Advanced and characteristic lesions were observed more often in the white than in the negro group.

An interesting observation in this study was the high incidence of nutritional deficiency in association with certain diseases. All persons with hyperthyroidism, cirrhosis of the liver and chronic

alcoholism and two-thirds of the patients with severe infections, diabetes mellitus, carcinoma, and diseases of the gastro-intestinal tract had findings suggesting vitamin deficiency.

The research program of the Department of Medicine at Tulane University has included the study and development of laboratory tests for the evaluation of human nutritional status. The earliest investigations dealt with ascorbic acid. Of 133 patients attending a medical clinic, 86 were found to have a level of plasma ascorbic acid of less than 0.4 mg. per cent. The urinary excretion of ascorbic acid, and the amount in the blood plasma, were determined in a number of persons after oral or intravenous administration of large amounts of this vitamin (8). These "saturation" tests indicated that many members of the clinic and hospital population had depleted bodily stores of ascorbic acid. Eighteen patients with pellagra (9) were studied in this manner and 12 had evidence of ascorbic acid deficiency, which observation emphasizes the accepted concept that deficiency states are usually multiple. Vitamin C deficiency occurred with great frequency in association with allergic states, especially bronchial asthma, and prolonged study of a group of individuals with this disease indicated that the requirement of ascorbic acid was higher than normal (10).

The urinary excretion of niacin and its derivatives was studied in a group of normal persons, in hospitalized patients with various acute and chronic diseases and in patients with clinical evidence of pellagra, ariboslavinosis and thiamine deficiency. The findings were reported by Goldsmith (11) in a recent publication. A low excretion of niacin derivatives was found not only in patients with pellagra and vitamin B complex deficiency, but in a number of hospitalized patients in whom there was no clinical evidence of deficiency of niacin. The administration of 300 mg. of nicotinamide followed by the determination of the excretion of niacin derivatives for a six hour period was suggested as a useful procedure in evaluating nutritional status in regard to this vitamin.

Several problems are being currently investigated in the nutrition laboratory at Tulane University. The levels of lactic acid and pyruvic acid in the blood and the lactate-pyruvate ratio have been determined in various physiologic and pathologic states (12). Numerous factors have been found to influence the lactate-pyruvate ratio including exercise, food, anoxia and thiamine deficiency. The fall in the ratio when there is an inadequate supply of thiamine, does not occur early enough to be of clinical value in diagnosing mild thiamine deficiency. Determination of the ratio appears to be a useful procedure in studying

certain aspects of thiamine and carbohydrate metabolism when experimental conditions are rigidly standarized.

The excretion of thiamine, riboflavin and F<sub>2</sub> (N methyl nicotinamide or derivative) in the urine is being measured in normal persons and in patients with mild and severe deficiency disease. Determination of the excretion of these three substances in a one hour urine specimen, collected in the morning after a twelve hour fast, was suggested by Holt and Najjar (13) as a simple method for the laboratory diagnosis of deficiency of thiamine, riboflavin and niacin. This test has been performed in over 100 persons and appears to be helpful in evaluating the adequacy of nutrition in regard to these vitamins.

During the past six months a study of the nutritional status of pregnant women has been in progress in East Baton Rouge, Plaquemine and St. Landry parishes in Louisiana. This investigation was initiated by the Louisiana State Board of Health in cooperation with the Department of Agricultural Chemistry and Biochemistry of the Louisiana Agricultural Experiment Station, the Department of Home Economics of the Louisiana State University, and the nutrition laboratory of the Department of Medicine of Tulane University. Women who were attending prenatal clinics of the State Health Department or who were being cared for under the Emergency Maternal and Infant Care Program, and others, were examined during the second and third trimesters of pregnancy. The study has included 1, a dietary history; 2, kodachrome photographs of the face, eyes, lips, tongue, gums, hands and skin of the lower extremity; 3, determination of hemoglobin, volume of packed erythrocytes, serum proteins and ascorbic acid in the blood; and 4, estimation of the excretion of thiamine, riboflavin and F<sub>2</sub> (N methyl nicotinamide or derivative) in a one hour specimen of urine collected before breakfast.

Up to the present time seventy-two women (42 white—30 negro) have been studied. The major portion of the investigation has been carried out by Purdy<sup>1</sup> in collaboration with Moore<sup>2</sup>, Hollinger

*et al.* who have assisted in the planning and in analysis of data. Goldsmith and associates (15) determined the urinary excretion of the B vitamins. The dietary history, obtained by Purdy, consisted of a complete record of all food eaten for a period of one week. During this time all portions of food served were measured, the quantities as well as the methods of preparation being checked by frequent visits to the home. Analysis of the diets in terms of essential nutrients has not been completed but preliminary evaluation shows that a majority of the diets fail to measure up to National Research Council recommendations, while a few are severely deficient in one or more food factors. Purdy (14) found that 25 of the 72 women had a level of ascorbic acid in the blood plasma of less than 0.2 mg.%; an additional 22, a level of less than 0.4 mg.%. Serum proteins measured less than 5 grams per 100 c.c. of blood in one case; 5-5.5 gm. in 10; 5.5-6 gm. in 14 and over 6 gm. in 47. The hemoglobin in the blood was found to be less than 10 gm. per cent in 12 women and between 10 and 11 gm. per cent in 21.

Goldsmith found that the excretion of the B vitamins in the urine, in one hour during fasting, was low in a number of instances. While normal values for this test have not been definitely established, the following findings represent excretions lower than any obtained in healthy individuals on a good diet. The excretion of thiamine in one hour was less than one microgram in 5 women and between one and two micrograms in eight. Riboflavin excretion was less than 10 micrograms in 10 persons. The output of F<sub>2</sub> (expressed as N methyl nicotinamide) was zero in five instances and less than 50 micrograms in four. These data will be discussed in detail elsewhere in connection with other studies of the urinary excretion of the B vitamins (15). The findings obtained from dietary histories, photographs and laboratory tests in this group of pregnant women will be correlated and reported in detail by Purdy (16) and her associates. Plans have been formulated for continuing this investigation of nutrition in pregnancy in other parts of Louisiana.

This brief review of the dietary, clinical and laboratory studies which have been carried out in New Orleans and Louisiana indicates that nutritional deficiency is still an important problem in this part of the country. Further investigations are contemplated and remedial measures will be instituted. A clinic has recently been established in the department of Medicine at Tulane University for the study of nutritional and metabolic disorders. This clinic should be of assistance in research, in teaching and in the therapeuticis of nutritional deficiencies.

<sup>1</sup> Purdy, Maud B., Graduate Fellow, Department of Agricultural Chemistry and Biochemistry, Louisiana Agricultural Experiment Station and Department of Home Economics. Work supported in part by a grant from the General Education Board.

<sup>2</sup> Moore, Margaret C., Consultant on Nutrition, Louisiana State Department of Health, Hollinger, Martha, Associate Nutritionist, Department of Agricultural Chemistry and Biochemistry, Louisiana Agricultural Experiment Station and Department of Home Economics.

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## MICROCHEMICAL METHODS FOR NUTRITIONAL STUDIES

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One of the most important needs in the field of nutrition, and one which has been receiving considerable attention lately, is the development of more adequate and more quantitative knowledge concerning the relation of nutrition to health.

It has been evident for some time that the benefits to be derived from good nutrition are much broader than the prevention of deficiency diseases. Progressive improvements in growth, development, resistance to infection, and general health beyond that generally accepted as normal can be obtained by the betterment of nourishment over a wide range. However, the nature and degree of the benefits which a population such as that of the United States might expect to derive from a higher nutritive level, the value of these benefits in terms of the whole health picture, and in terms of practicability and cost are questions which cannot be answered satisfactorily on the basis of present incomplete knowledge.

One of the important aspects of this complex and difficult problem of evaluating nutrition in terms of health is the necessity of finding more adequate and practical methods for measuring nutritional status (in terms of essential nutrients) on individuals and large population groups. The use of dietary histories for this purpose is in most cases impractical and filled with uncertainties. Likewise, the use of the chemical methods previously available has had many disadvantages.

It is impractical, for instance, to obtain blood samples for survey purposes by venipuncture. This procedure which has been necessary because of the large specimen of blood required (25 to 30 cc.) is not only laborious, but so disturbing to the subjects that their co-operation is soon lost. The same objections can be made to procedures requiring fasting or timed urine specimens. In addition to the difficulties involved in obtaining specimens, these macromethods are usually so laborious from a laboratory point of view that their use for large scale survey purposes or for extensive physiological studies is greatly limited because of the time required. If, however, the above mentioned difficulties could be overcome, biochemical methods offer possibilities as direct objective means for measuring the dietary intakes of the various nutritive essentials.

Some time ago this laboratory undertook the problem of developing microchemical methods which might be suitable for the determination of the various important nutritive substances in blood and other body fluids. It was hoped that methods could be developed for which the amount of blood obtainable from a simple finger-tip puncture would be sufficient for several different determinations. Encouraging progress has been made in finding such methods.

We now have in use in our laboratory micro-methods for seven of the nutritive essentials or their corresponding tissue derivatives. These

methods have been thoroughly tested for reproducibility and accuracy against the usual macro-methods and by other standards, and they are very satisfactory in this respect. They have also had a limited field test on about 1,000 New York school children, which has demonstrated the simplicity of obtaining and preserving specimens, and the rate at which the determinations can be performed in the laboratory. The seven substances (vitamin A, carotene, ascorbic acid, riboflavin, serum protein, hemoglobin, and alkaline phosphatase) can be determined on two or three drops (0.1 ml.) of blood. Details of the methods and proof of their reliability will be published in a series of papers which are being prepared. Therefore, only a brief description of the procedures and mention of the equipment used will be presented here.

The blood, 0.1 ml., is collected from a finger-tip puncture in two capillary tubes, 50 emm. of blood in each. Tubes of the type used for melting point determination are used. One tube contains an anticoagulant (heparin) while the blood in the other is allowed to clot. After filling, the ends of the tubes are sealed with Plicene cement, labeled, and sent to the laboratory. Two workers can collect about forty specimens an hour. The procedure is simple and expedient, and even small children do not object to repeated testing.

In the laboratory, the capillary tubes are centrifuged (several hundred at a time), after which the tubes are broken with a diamond pencil at the junction between the fluid and cellular layers. Aliquots are removed for the various determinations by the use of Lang-Levy pipettes (1). These pipettes can be made to deliver volumes of 3 emm. to 1,000 emm. with an accuracy of 0.05 to 0.5 per cent. They are filled and delivered by the use of a small rubber tube of the type used with blood cell pipettes. With these pipettes one can not only measure small volumes of fluids with a high degree of precision, but the measurements can be made much more rapidly than with pipettes of the usual type and volume.

Vitamin A and carotene are determined as follows: 35 emm. of plasma are measured into a capillary test tube. Alcoholic KOH is added and the tubes are incubated for a few minutes for saponification. An accurately measured volume of xylene-kerosene mixture is then added plus a short piece of steel wire, and the tube is sealed in an open flame. The vitamin A and carotene are extracted by shaking a number of the tubes at the same time. After centrifuging, the tube is broken and the xylene-kerosene layer transferred, by the use of a micropipette, into a microcuvette. The light absorption at 460 m $\mu$  is used as a measure of the carotene while the absorption at 328 m $\mu$ , before and after irradiation of the sample in ultraviolet light (which destroys vitamin A) is used

to determine vitamin A. The Beckman spectrophotometer has been adapted and cuvettes designed so that colorimetric measurements can be made on 30 to 50 emm. of solution. Two persons can do about 100 such vitamin A determinations in a day.

Plasma ascorbic acid is determined on 10 emm. of plasma. The Roe method (2) which involves the determination of the color resulting from the reaction of dehydroascorbic acid with dinitrophenyl hydrazine has been used. The color is measured with the Beckman spectrophotometer as indicated above. Two technicians can perform approximately 150 such determinations per day.

Riboflavin is determined in the red blood cells (20 emm.) by means of a microbiological method suitable for use with 0.1 to 0.5 m $\mu$ g. of riboflavin. The details of this procedure as used on corneal tissue has recently been published (3).

Since the density of plasma is primarily due to its protein content, a density measurement can serve as a means of determining plasma proteins. For this purpose the Lang gradient tube has been used (4). The gradient tube is prepared as follows: A 1,000 ml. graduate cylinder is half filled with brombenzene-kerosene mixture, density 1.07; a kerosene-brombenzene mixture, density 0.99, is carefully layered above. The two layers are then mixed by a churn-like motion with a stirrer in such a manner that a column of varying density results, heavy at the bottom and progressively less dense up the length of the column. An aqueous drop placed into such a column falls until it reaches a position of equidensity. This position can be read from the graduations on the cylinder. The column is calibrated with salt solutions of known density before each series of determinations. As many as 50 to 70 determinations can be made in duplicate before it is necessary to remove the plasma droplets. This is quickly done by sprinkling a small amount of sea sand into the cylinder, which adheres to and carries to the bottom the aqueous drops. A gradient of this type remains usable for six to eight months. The method is simple and accurate, as shown by comparison with the Kjeldhal method (4). A team of two people can do 60 or 70 determinations per hour by this method.

Hemoglobin is determined colorimetrically. At the time the blood is collected, a 5 to 10 emm. specimen, measured accurately by means of a constriction pipette, is delivered directly from the finger into 1 ml. of dilute ammonia. The color density is subsequently measured in a photoelectric colorimeter. If the blood is carefully drawn, this method has a precision of  $\pm$  2 to 3 per cent. It is of interest to point out that although hemoglobin methods have been extensively used for some years, much of the data in the literature can-

not be compared because of the failure to use standard and precise methods.

Phosphatase is determined by the use of a newly developed, simple, and direct method. Three cmm. of serum are measured into a small tube. Fifty cmm. of a reagent composed of 0.4 per cent of the sodium salt of p-nitrophenyl phosphate in a buffer are added. The tube and contents are incubated at 37° C. for thirty minutes, and 0.4 ml. sodium hydroxide is added to stop the reaction. The yellow color produced by the p-nitrophenol resulting from hydrolysis of the colorless phosphate reagent is measured in a photoelectric colorimeter. Several hundred determinations can be completed in a day by two technicians.

These microchemical techniques offer an advantage not only in regard to the convenience of procurement of specimens, but also in the rate at which determinations can be performed in the laboratory. It should be pointed out that for

large numbers of specimens offers no difficulties and proceeds with good economy of time. Likewise the precision of analysis under such circumstances was satisfactory. Figures 1 and 2 summarize the results of determinations of ascorbic acid and hemoglobin on three groups of New York school children (A, B, and C), all with different economic backgrounds, and illustrate how the methods may be used for group studies. Each group numbered about 75; group A—from a high economic area of the City, group B—from an area of intermediate economic circumstances, and group C—from a very low economic area. The points on each of the curves show the percentage of each particular group which had analytical values falling in the zone indicated by the figures along the base of the curve. For instance, in figure 1, 60 per cent of group A had plasma ascorbic acid levels of 1.5 to 2.0 mg. per cent, while only 5 per cent of those in group C had ascorbic acid values in the same

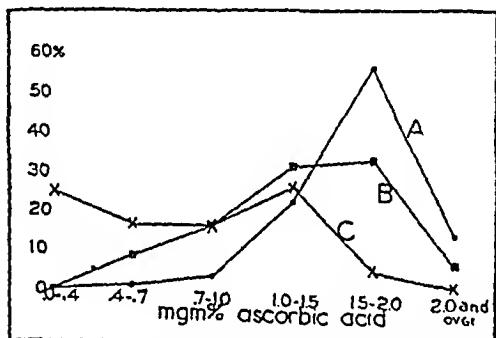


Fig. 1. Distribution of plasma ascorbic acid analysis. Group A—well nourished; Group B—intermediately nourished; Group C—poorly nourished (see text).

some methods instruments are used which cannot be easily taken into the field (e.g. the Beckman spectrophotometer). However, with present-day transportation methods it is no longer necessary to plan to do all determinations in the field. One of us (O. H. L.) used the described micromethods recently as a part of a survey in Newfoundland. (5). A kit weighing less than 100 pounds was all that was required in the field. Some of the determinations were made there while other specimens were prepared for shipment in dry ice to the laboratory. (Small volumes make this a practical procedure.) Several weeks elapsed before some determinations were done. This was made possible by the proper preservation of the specimens before freezing.

A full report on the results of surveys in which these micromethods have been used is in preparation and, therefore, only a brief comment on this material will be made here. The analysis of

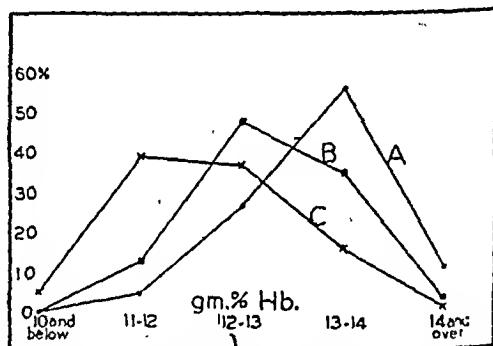


Fig. 2. Distribution of hemoglobin analysis. Group A—well nourished; Group B—intermediately nourished; Group C—poorly nourished (see text).

range. Although there were no children in group A having an analysis below 0.4 mg. per cent (considered a subnormal level) 25 per cent of the children in group C were below this level. It is interesting to note that the hemoglobin values (fig. 2) show a similar distribution. The same has been found to be true for vitamin A and carotene.

Among these groups there were similar measurable differences in the blood values for many of the essential nutrients. This undoubtedly means a difference in nutritive level. What these differences mean in terms of health is, of course, another problem.

Although in general there is a correlation between the dietary intake of the various nutritive essentials and the concentration of these substances or their derivatives in the blood and body fluids, there are other factors which also influence these concentrations. Furthermore, the blood and tissue levels may not bear a linear relationship to

the intake over a broad range. It is, therefore, necessary in order to interpret blood analysis in terms of dietary intake or nutritional status to have certain information concerning the physiology and biochemistry of these substances. Much of the necessary information is now at hand, but it is clearly necessary to obtain further knowledge of the processes involved in order to derive full value from blood data. The availability of the micro-analytical methods described here should be of assistance in obtaining the kind of information needed for the reliable interpretation of such data.

In addition to application to surveys, there are other advantages in the use of micromethods. There are many nutrition problems in pediatrics, particularly in connection with the premature infant, which will be made possible or easy by such methods. There is much to be learned about the physiology of the various nutritive essentials which can come through further studies with experimental animals. With micromethods available, repeated blood samples may be obtained from the

same small animal, thus avoiding the necessity of using pooled samples. Such methods also make possible studies on very small biopsy specimens from either man or experimental animals. Thus certain tissue studies heretofore impossible become feasible.

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### FINDINGS ON EXAMINATIONS OF NEWBORN INFANTS AND INFANTS DURING THE NEO-NATAL PERIOD WHICH APPEAR TO HAVE A RELATIONSHIP TO THE DIETS OF THEIR MOTHERS DURING PREGNANCY

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In considering the evidences of faulty nutrition which may be observed at the time of birth, I am going to pass over the well-known evidences of deficiency diseases and take up some rather special evidences which have come to light recently and are not usually associated with the question of prenatal nutrition.

Of course, most of the nutritional deficiency diseases have been reported at birth, but they are very seldom encountered at that particular stage. When they are encountered at three months or even six months, they probably reflect faulty maternal nutrition. But I am concerned here primarily with a few types of evidence which can be recognized at birth and which seem to reflect faulty maternal diet.

I shall present at first a few charts which show the background of what I want to summarize at the end as to the newer evidences. As the time is short, I am going to assume that most of you are familiar with what the Department of Maternal and Child Health of the Harvard School of Public Health has been doing at the Lying-in-Hospital in

Boston and with the publications of Mrs. Burke and the others that have thus far appeared; but to orient you, I shall show three or four charts from publications that have already appeared.

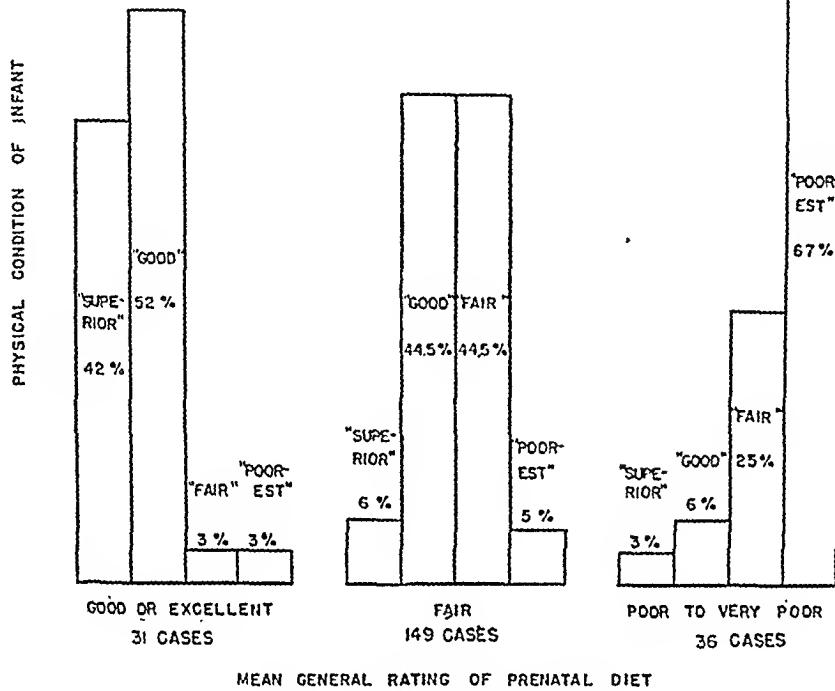
I might say that we felt some years ago when we started these studies that we wouldn't get very far unless we had a triumvirate working together: a nutritionist, an obstetrician and a pediatrician. Unfortunately, Doctor Kirkwood, our obstetrician, has been in the Army for more than two years, I have been away for the major portion of the last two or three years, and Mrs. Burke has been carrying on valiantly alone—rather, with the aid of others who have come to her assistance at the School of Public Health.

Figure 1: I am not going to take time to define terms which have been defined in the publications. This chart shows what Tisdall and others have shown before, that there is a marked relationship between condition at birth in general and dietary inadequacies in general. Since my return, Mrs. Burke and I have been attempting to assemble data which will give us a little better idea as to

the specific signs in the infant and as to the specific factors in the diet.

Figure 2: This shows maternal diet, that is, the general rating of maternal diet in relation to birth

Figure 3: You will see from this chart that in the good to excellent diet group there are very few small babies, and most of them are in the over seven pounds group; whereas the reverse is



Courtesy of The Journal of Nutrition, 26, p. 569, December, 1943

Fig. 1. Relationship of prenatal nutrition to the physical condition of the infant at birth and within first two weeks of life.

#### *Birth weights and lengths of infants grouped according to prenatal dietary rating*

BIRTH WEIGHT lbs.-oz.	PRENATAL DIETARY RATING		
	Excellent or good	Fair	Poor to very poor
Average.....	8-8	7-7	5-13
Range.....	6-12 to 11-7	3-6 to 9-3	3-4 to 8-15
BIRTH LENGTH cm.			
Average.....	51.8	50.0	47.2
Range.....	46.9 to 54.6	45.0 to 54.4	40.6 to 52.7

Fig. 2—Courtesy of the Journal of Nutrition, 26, p. 569, December, 1943

weight and birth length. Prematures have been included in this chart, so that factors of small size that are contributed by premature onset of labor as well as by faulty fetal growth can be taken into account.

true for the poor diet group. The same is shown for body length at the bottom of the chart. There are few infants under 50 centimeters in the good diet group and few over 50 centimeters in the poor diet group.

Figure 4: This chart shows the relation of protein in the maternal diet to birth length. It appears that the length of the baby at birth is very closely associated with the amount of protein in the mother's diet.

Figure 5: This gives the numerical values for the data presented in graphic form in the preceding chart, excluding premature infants. We have found a higher correlation between animal protein (excluding milk and cheese) and length, than be-

maternal diet and osseous development at birth and is a very interesting recent finding in analyzing our material. By ossous development I mean the presence of osseous centers in the hand, knee, and foot, based upon study of X-rays taken at birth. Mrs. Harding of our Department has given a rating of "advanced", "average" or "retarded" to all the X-ray films taken on this group of infants. You see that generally poor diet is strongly correlated with retardation in the in-

*Birth weight and birth length in relation to maternal diet during pregnancy  
(From study of 216 pregnancies, Harvard School of Public Health series)*

BIRTH WEIGHT	MATERNAL DIET RATING				
	Good or excellent	Fair to good	Fair	Fair to poor	Poor to very poor
	Number of cases				
	31	36	63	50	36
3 to 5 lbs.....	0	1	0	0	8
5 to 7 lbs.....	2	6	16	16	19
7 to 9 lbs.....	20	27	46	34	8
9 to 11 lbs.....	8	2	1	0	0
11 lbs. plus.....	1	0	0	0	0
Unknown.....					(1)
Total under 7 lbs.....	2 (6%)	7 (19%)	16 (25%)	16 (32%)	27 (77%)
Total 7 lbs. and over.....	29 (94%)	29 (81%)	47 (75%)	34 (68%)	8 (23%)
BIRTH LENGTH					
42 to 44 cm.....	0	0	0	0	2
44 to 47 cm.....	0	2	0	5	8
47 to 50 cm.....	3	6	23	27	13
50 to 53 cm.....	21	25	39	18	6
53 cm. and over.....	7	3	1	0	2
Unknown.....					(5)
Total under 50 cm.....	3 (10%)	8 (22%)	23 (36.5%)	32 (64%)	23 (74%)
Total 50 cm. and over.....	28 (90%)	28 (77%)	40 (63.5%)	18 (36%)	8 (26%)

Fig. 3

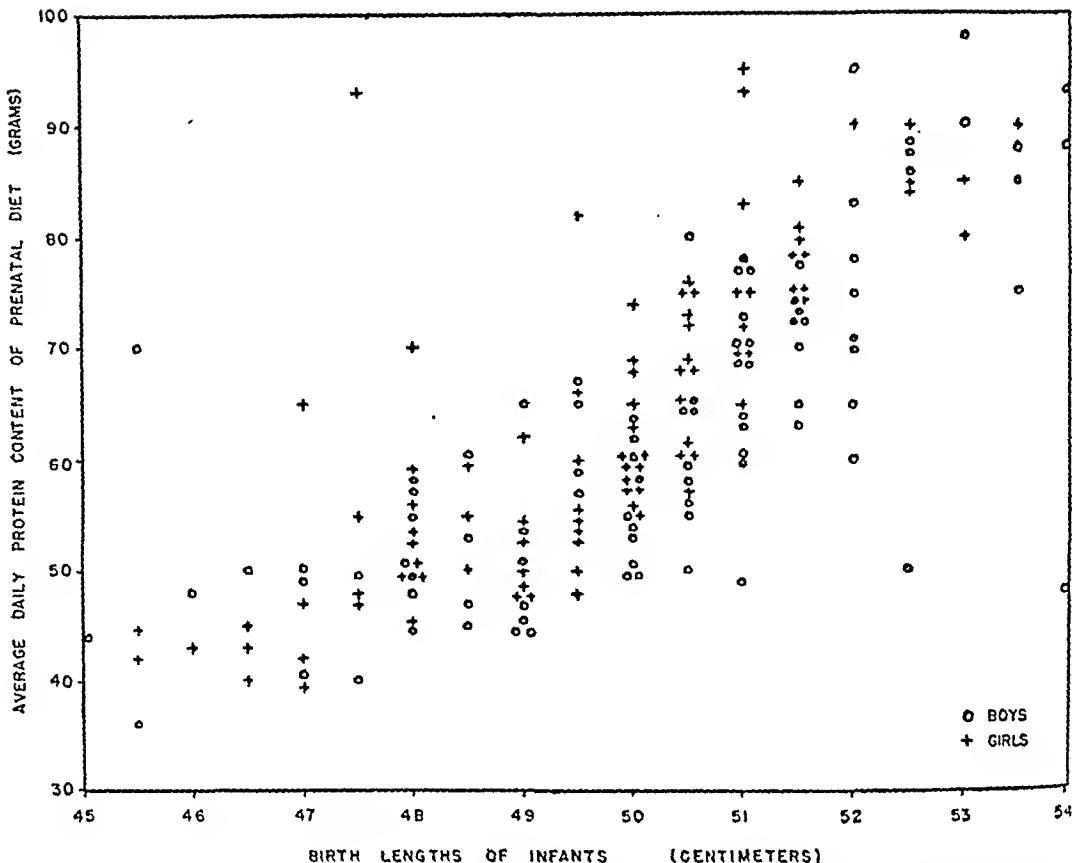
ween either total non-animal protein or milk alone and length.

The relation between maternal diet and the mount of muscle and subcutaneous tissue in the infant would be of interest. This could unquestionably be learned from X-ray films of the leg of the infant. One of us has demonstrated the value of such a technique at other ages, but unfortunately our X-rays taken at birth were not planned with this in mind. So few of them are good that I am not able to give you the evidence from our own particular studies.

Figure 6: This chart shows the relation between

fant's osseous development. The difference between a good or excellent diet and a fair diet is not so striking, although there are more retarded infants in the fair diet group. It is obvious that few are advanced and many are retarded in the very poor diet group.

We have studied the same subject from the standpoint of the protein in the maternal diet and find what appears to be an even stronger relationship, which is shown in Figure 7. We realize that protein, phosphorus and certain other nutrients are closely associated in the diet and that it might be one or another factor when protein is studied.



Courtesy of The Journal of Pediatrics, 23, p. 506, November, 1943

Fig. 4

*Relationship of birth weight\* and birth length to total protein in mother's diet during pregnancy (4th through 9th month)*

	AVERAGE TOTAL PROTEIN (GM.)					
	Under 45	45 to 54	55 to 64	65 to 74	75 to 84	85 or more
Birth weight in pounds and ounces						
Boys....	6-8	7-0	7-7	8-0	8-5	9-2
Girls....	5-14	6-14	7-8	7-12	8-1	8-8
Birth length in centimeters						
Boys....	47.6	49.3	50.2	51.4	52.0	53.3
Girls....	46.8	48.7	49.9	50.3	51.4	52.4

\* No infants under 5 pounds were included in this distribution.

Courtesy of The Journal of Pediatrics, 28, p. 506, November, 1943

Fig. 5

However, we know that protein forms the matrix for bone growth, and there are other evidences that protein may be the principal factor here. In the excellent protein diet group, 57 per cent were advanced and 14 per cent were retarded, whereas

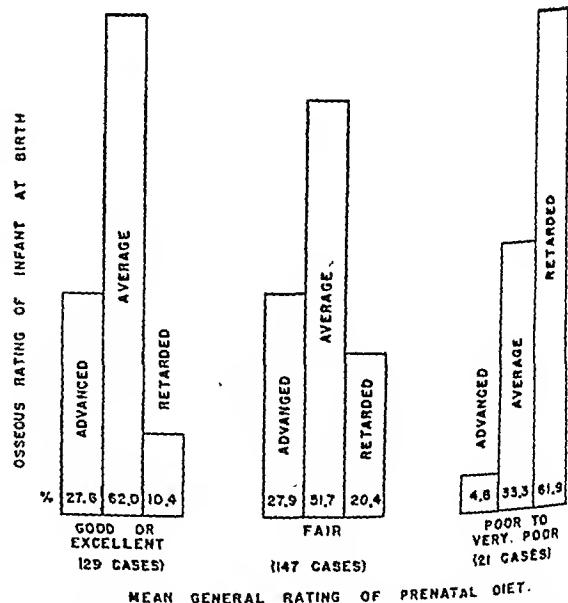


Fig. 6. Relation of osseous development of living full-term infants at birth to their mothers' diets during pregnancy.

in the poor protein group none were advanced and 71 per cent were retarded in osseous development.

We have examined our data on osseous development from the standpoint of calcium in the diet. This relationship is shown in Figure 8. A some-

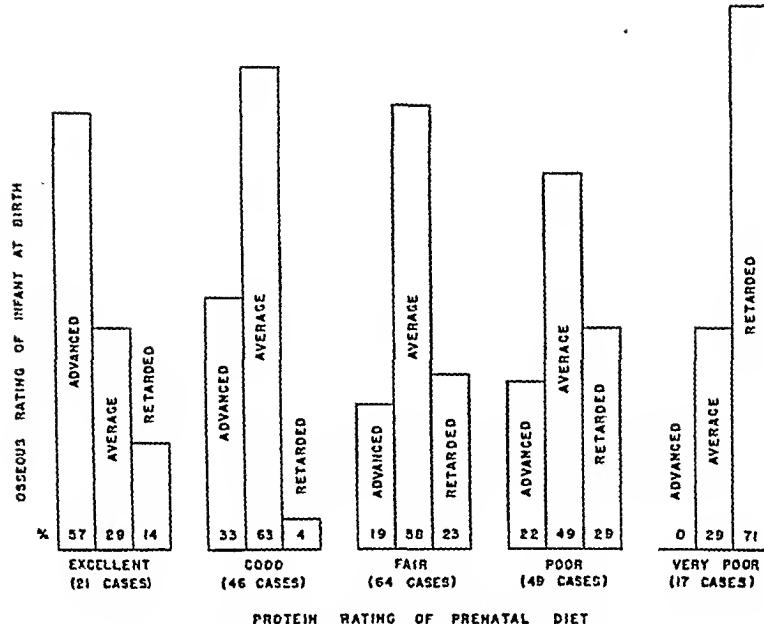


Fig. 7. Relation of osseous development of living full-term infants at birth to the protein content of their mothers' diets during pregnancy.

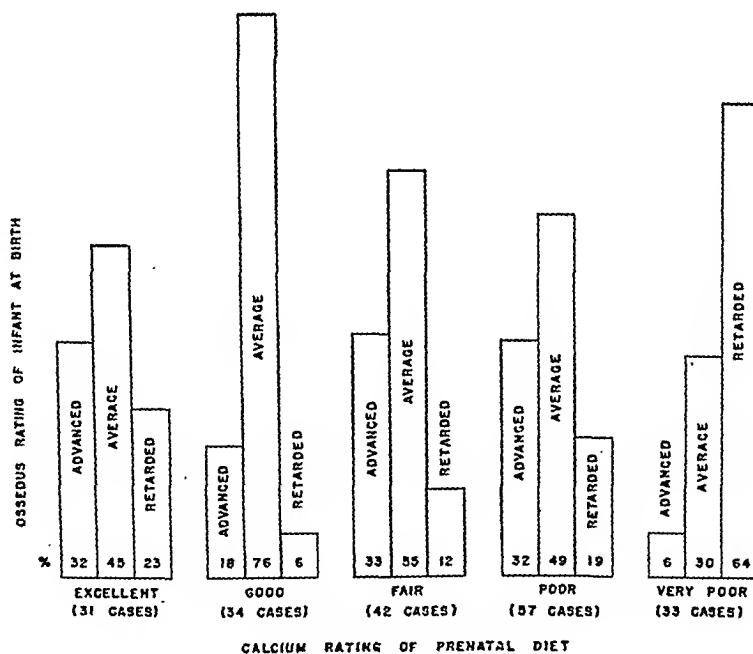


Fig. 8. Relation of osseous development of living full-term infants at birth to the calcium content of their mothers' diets during pregnancy.

what less marked relationship was found than with protein; excellent calcium giving 32 per cent advanced with 23 per cent retarded, poor calcium

giving 6 per cent advanced and 64 per cent retarded.

Mrs. Harding has devised a technique for eval-

uating the amount of calcium in the teeth as seen in the lateral roentgenogram of the head at the time of birth. She made ratings of all of our infants independently on the basis of her technique. (Figure 9.) This slide shows very much the same relationship between calcification in the teeth before eruption and maternal diet as obtained for osseous development in the bones. There were no advanced and a very large number of retarded in the poor diet group. As to protein in the mother's diet in relation to calcification of the teeth (Figure 10), 37 per cent in the excellent protein group showed advanced tooth development, 16

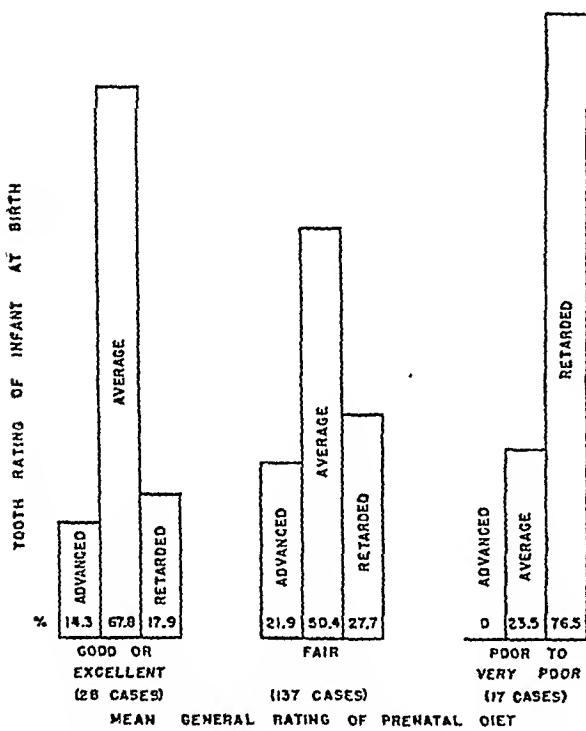


Fig. 9. Relation of development of teeth (as seen in lateral X-ray of head) in living full-term infants at birth to their mothers' diets during pregnancy.

per cent retarded; whereas in the very poor protein group, none were advanced and 71 per cent were retarded. For the excellent calcium diets, 28 per cent of the infants were advanced and 24 per cent retarded; for the very poor calcium diets, 10 per cent were advanced and 62 per cent retarded. This relationship is shown in Figure 11.

I am going to pass over the question of blood values because we didn't have satisfactory blood determinations for the newborn on a large enough number of this series to be sure what sort of relationship existed. We believe that blood hemoglobins and red counts are of much more significance at three months or even at six months than they are at birth in relation to maternal diet. We will later consider the relation of maternal anemia to infant conditions.

Figure 12: In order to understand why so many infants are in unsatisfactory condition at birth when their mothers have taken a poor or very poor diet during pregnancy, it is necessary to consider the health and associated findings of the mother. This slide shows the general maternal dietary rating in relation to the complications of pregnancy occurring in 80 of these 216 women. Pre-eclampsia occurred 28 times, severe nausea and vomiting 16 times, severe anemia 11 times. There were 46 complications in the miscellaneous group, and most of them were mild or minor conditions which would not be expected to influence the fetus in any way. So, I shall confine my attention to the three groups: pre-eclampsia, nausea and vomiting, and anemia.

Figure 13: Here we see that 23 of 28 infants born to women with pre-eclampsia failed to obtain a good rating. Among the poor results were 2 stillbirths, 3 premature births with congenital defects, 4 premature births without congenital defects, 9 immature births<sup>1</sup> and 5 with other conditions which contributed to a pediatric rating of fair or poor. One of the stillborn infants had multiple congenital defects as well. Thus 4 infants in this series of 28 had congenital defects. Pre-eclampsia doesn't occur early in pregnancy, and congenital defects obviously are initiated early in pregnancy. So we can't say that the pre-eclampsia was the cause of the congenital defect, but it might be that faulty diet before or during early pregnancy led to the congenital defects or to some of the congenital defects as well as to the pre-eclampsia.

Figure 14: This chart is too complicated for hasty review, but under the good or excellent diet heading we see that there were no cases of pre-eclampsia. There were 12 cases of pre-eclampsia in the fair diet group and 16 in the poor to very poor diet group. The slide shows that pre-eclampsia in a number of cases led to early interruption of pregnancy, and this explains in part the incidence of prematurity in this series. There was also considerable dystocia both in those having spontaneous onset of labor and in those in which labor was induced, possibly more than would be expected in such a series.

Figure 15: In the 16 cases of complication with severe nausea and vomiting, one in the fair diet group and five in the poor diet group later had pre-eclampsia. If we eliminated these, we find that nausea and vomiting occurred in almost the same numbers among women taking good, fair and poor diets, but what happened to the baby differed considerably. It appears that poor diet

<sup>1</sup> By "immature" is meant that the infants received a "functionally immature" rating from the pediatrician and were in the borderline weight group between 5 pounds and 6 pounds, 8 ounces.

per se may not contribute to the occurrence of severe nausea and vomiting but if the latter is but succeeds in taking an adequate diet during pregnancy, there doesn't appear to be a strong

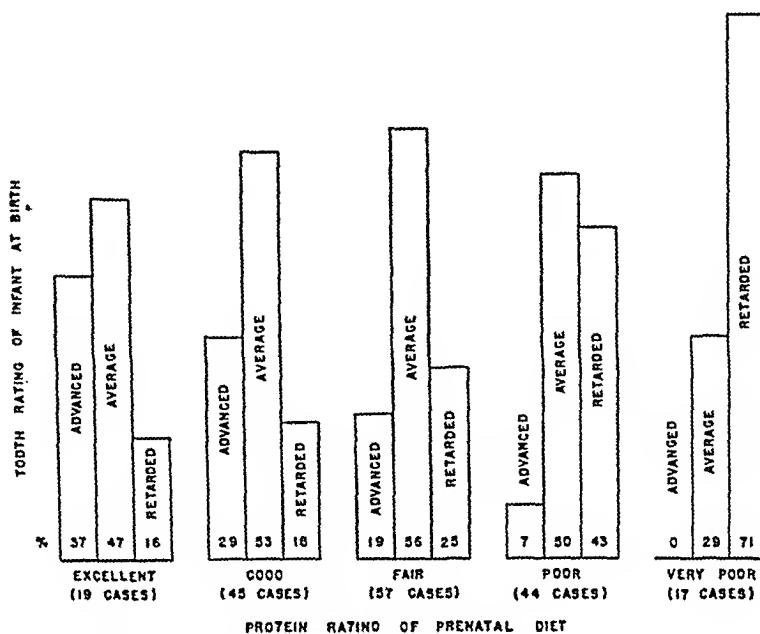


Fig. 10. Relation of development of teeth (as seen in lateral X-ray of head) in living full-term infants at birth to the protein content of their mothers' diets during pregnancy.

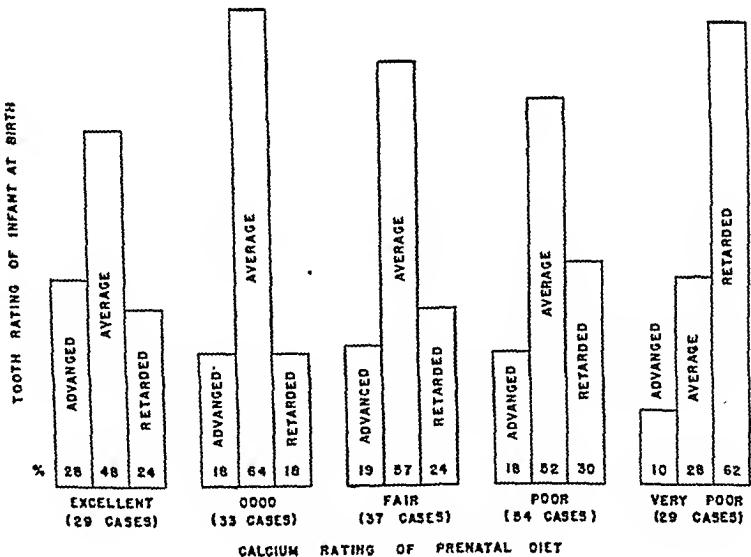


Fig. 11. Relation of development of teeth (as seen in lateral X-ray of head) in living full-term infants at birth to the calcium content of their mothers' diets during pregnancy.

severe, it may lead to a poor diet being consumed during pregnancy and this may in turn lead to the conditions associated with inadequate diet. In other words, if a woman has nausea and vomiting

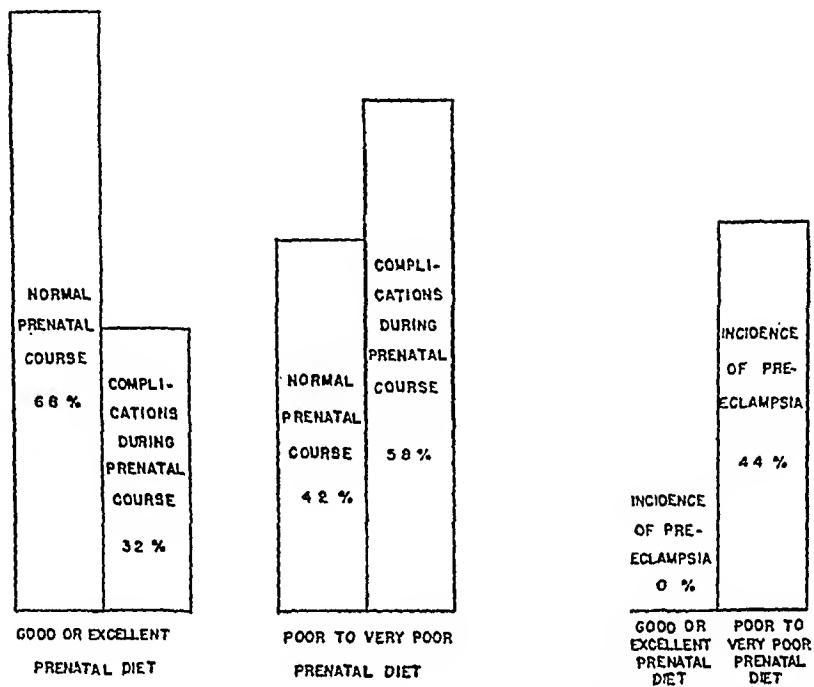
relationship between nausea and vomiting per se and unsatisfactory condition of the infant at birth.

Figure 16: This is a very complicated chart, but I would simply call your attention to the fact

that among 11 cases of severe anemia occurring among 216 mothers, 6 of the infants obtained a good or excellent rating at birth, against 5 who did not. There was one stillbirth in this group with multiple congenital anomalies, and there was one

was an unduly high incidence of unsatisfactory condition.

Premature birth and functional or structural immaturity at birth appear to be to an important extent related to faulty maternal diet, either



Courtesy of American Journal of Obstetrics and Gynecology, 46, p. 38, July, 1943

Fig. 12. Relationship of the prenatal course to the mother's diet during pregnancy. Incidence of pre-eclampsia in relation to the mother's diet during pregnancy.

*Condition of infant at birth following 28 pregnancies complicated by pre-eclampsia*

(From study of 216 pregnancies, Harvard School of Public Health series)

CONDITION OF INFANT AT BIRTH	NUMBER OF CASES	PER CENT
Stillborn.....	2	7
Premature with congenital defect....	3	11
Premature without congenital defect....	4	14
Immature (5-1 to 6-8).....	9	32
Condition "fair" or "poor" for other reasons.....	5	18
Total failing "good" rating.....	23	82
Infants in "good" condition.....	5	18
Infants in "excellent" condition...	0	0

Fig. 13

immature birth, and three infants had other pathological findings. One of these eleven women had pre-eclampsia. This slide shows that although a number of the infants born to these anemic women were in good condition at birth, there

directly or indirectly. Thus faulty prenatal nutrition should be looked upon as one of the possible causes of small size or immaturity at birth. Clinical evidences of immaturity should be supplemented with body measurements and a rating of osseous development at birth. Development of the primary teeth, as seen in X-ray films of the head, may prove to be a helpful indication as well. The protein content of the mother's diet appears to be a particularly important factor in relation to the maturity of the baby at birth and in relation to his body size. Congenital defects of the types which represent retarded or faulty embryonic development should be looked upon as possibly the result of faulty maternal nutrition and therefore should be rerecorded under a nutritional examination of the newborn. It should be remembered, however, that preconceptional diet and diet in the early months of pregnancy are probably more important than diet in later pregnancy in leading to congenital defects.

A nutritional assessment of the newborn should include in the questionnaire the occurrence of pre-eclampsia, pernicious vomiting or severe anemia during pregnancy, and it probably should also include evidence of dystocia due to uterine

inertia and the like, but we have very little evidence on that subject as yet. The weight of the mother at the beginning and the end of pregnancy

On the basis of present knowledge, a survey of the nutritional state of the population should include observations on four special groups in

*Study of 28 cases of pre-eclampsia in relation to maternal nutrition*

(From study of 216 pregnant women and their infants, Harvard School of Public Health series)

	GOOD OR EXCELLENT DIET (31)	FAIR DIET (149)		POOR TO VERY POOR DIET (36)	
		Number of cases	Per cent	Number of cases	Per cent
Occurrence of pre-eclampsia...		12	8	16	44
Occurrence of fetal death...		0	0	2	6
Occurrence of neonatal death...		0	0	0	0
Occurrence of premature births 5 lbs. or less		1	0.7	6	18
Occurrence of immature births over 5 lbs. to 6½ lbs		3	2	6	18
Birth of congenitally defective (also premature) infants.....	No cases	1	0.7	2	6
Birth of infants with other or questionable pathology (classified as in "fair" condition)...		3	2	2	6
Birth of normal infants (classified as in "good" condition).....		5	3	0	0
Caesarian section.....		1	0.7	2	6
Induced labor with dystocia...		1	0.7	1	3
Induced labor without dystocia...		0	0	3	8
Spontaneous labor with dystocia.....		5	3	2	6
Spontaneous labor without dystocia.....		5	3	8	22

Fig. 14

*Condition of infant at birth following 16 pregnancies complicated by severe nausea and vomiting\**

(From study of 216 pregnancies, Harvard School of Public Health series)

	MATERNAL DIET GOOD OR EXCELLENT (31)		MATERNAL DIET FAIR (149)		MATERNAL DIET POOR TO VERY POOR (36)	
	Number of cases	Per cent	Number of cases	Per cent	Number of cases	Per cent
Occurrence of severe nausea and vomiting...	4	13	5	3	7	19
Occurrence of fetal death.....	0	0	0	0	1	3
Infants born prematurely.....	0	0	0	0	3	8
Occurrence of immature births (over 5 lbs. to 6½ lbs.).....	0	0	1	0.7	2	6
Birth of congenitally defective infants (one also premature).....	0	0	0	0	2	6
Birth of infants with other or questionable pathology (classified as in "fair" condition).....	1	3	2	1	0	0
Birth of normal infants (classified as in "good" or "excellent" condition).....	3	10	2	1	0	0

\* Pregnancy was later complicated by pre-eclampsia in six of these cases, one in the "Fair" diet group, five in the "Poor to Very Poor" diet group.

Fig. 15

is also important to the infant as well as maternal deficiency diseases. Clinical signs of specific deficiency disease are encountered rarely among newborn infants.

the population. If the fullest understanding of the influence of maternal dietary habits is to be obtained, suitable samples of the following groups should be selected:

First, married women of child-bearing age. These should reflect the dietary habits and nutritional state of women entering upon the long period of special requirements and strain of pregnancy and lactation. They reflect especially the conditions probably existing during the embryonic period, at which time congenital defects are, for the most part, in the making.

nutritional deficiency diseases have developed, and especially the incidence of pre-eclampsia, pernicious vomiting and anemia. The dietary histories and the blood levels at this time compared with those in the first group should indicate how successfully women have modified their customary diets in order to meet the exigencies of pregnancy.

*Study of 11 cases of severe anemia of pregnancy in relation to maternal nutrition and condition of infant at birth*

(From a study of 216 pregnant women and their infants, Harvard School of Public Health series)

	NUMBER OF CASES	MOTHER'S LOWEST HEMOGLOBIN gms.	IN-FANT'S LOWEST HEMOGLOBIN 1ST YEAR gms.	IN-FANT'S LOWEST R.B.C. 1ST YEAR millions	MATERNAL DIETARY RATINGS		
					Mean general	Iron	Protein
Occurrence of fetal death (multiple congenital anomalies)	1	8.1			Poor to very poor	Poor	Very poor
Occurrence of immature birth (5.1 to 6.8 lbs.)	1	6.1	8.0	3.15	Poor to very poor	Poor	Very poor
Birth of infants with other or questionable pathology (condition fair or poor at birth)	3	3.0 9.1 10.2	6.8 9.0	3.91 3.66	Poor to very poor Fair Fair	Very poor 7 months* then hospitalized Poor (to very poor) Fair (to poor)	Poor 7 months Poor Fair
Birth of infants in good condition	4	8.8 9.5 9.5 10.0	8.8 11.0 11.5 11.0	4.10 4.90 4.48 4.25	Fair Fair Good or excellent Fair	Fair (and med. iron) Fair (to poor) Poor 5 months then good Fair (to poor) and med. iron	Good Good Excellent Poor
Birth of infants in excellent condition	2	8.6 9.1	8.1 11.0	3.97 4.25	Poor to very poor Fair	Very poor Poor	Poor Fair

\* This was the only case among these 11 in which pregnancy was later complicated by pre-eclampsia.

Fig. 16

Doctor Spies has reported, as have others, on the much higher incidence of deficiency diseases among women, especially among women of child-bearing age. We want to be sure that the women of that age are not manifesting evidences of nutritional deficiencies.

Second, pregnant women during the last trimester of pregnancy. These should reveal how pregnant women have weathered the strain of pregnancy and in what numbers evidences of

Third, newborn infants. The usual search for signs of deficiency disease at this time will be very unproductive, and laboratory determinations are difficult to interpret. That is a very complicated question, which I won't discuss at this time. Diet histories will not be required if they have been taken on the first two groups. The principal items of interest at this time are evidences of defective embryonic and fetal development and of inadequate size or amounts of various tissues.

Fourth, infants at or about three months of age. Evidences of deficiency disease at this time are presumptive evidence of deficient nutritional state at birth, although a history of feeding since birth must be taken into account. A study at this time which measures osseous development, health, and growth progress since birth may still point to the influence of prenatal occurrences.

Just a word about further research on this general subject. We believe that the relationships between maternal nutrition and the condition of the infant at birth have only been touched upon thus far and need to be explored very much further. We are going ahead with new studies approaching the subject from a somewhat different angle. We are now taking women who develop toxemia and babies who are born dead or prematurely or with congenital defects or who die during the early days, and are obtaining dietary histories from the women concerned. We did this with some reluctance at first, fearing that it would be difficult to secure good histories, but we found that these women were interested and that they were able to give accounts of their eating habits which had every indication of being trustworthy, even for the period prior to the pregnancy concerned. We are also continuing to analyze the

material that we have at hand in the records of the series which has thus far been reported in part only.

We are planning, when personnel and time become available, to expand these studies in a number of ways. It is quite clear now that even though we have a great deal of information about our cases, our data are incomplete from the standpoint of what we would like to know. We certainly want more detailed search for evidences of malnutrition in the mother, including full laboratory determinations of her state before and during pregnancy. We want gross and microscopic studies of the placenta. We want studies of the cord and venous blood of the newborn in relation to the findings in the mother. We want absorption and tolerance tests in the newborn. We want thorough X-ray studies of the newborn and histories of forebears from the standpoint of information about the incidence of congenital defects in families. We want a complete review of the progress and physical findings of the infants at three months and at later ages, if possible, in order to be able to assess any evidences of deficiency diseases from the standpoint of possible faulty storage at the time of birth.

#### REFERENCES

- BURKE, B. S., BEAL, V. A., KIRKWOOD, S. B., AND STUART, H. C.: Nutrition Studies During Pregnancy. I. Problem, Methods of Study and Group Studied. II. Relation of Prenatal Nutrition to Condition of Infant at Birth and During First Two Weeks of Life. III. Relation of Prenatal Nutrition to Pregnancy, Labor, Delivery and Postpartum Period. Am. J. Obstet. and Gynec., 45, p. 33, 1943. BURKE, B. S., HARDING, V. V.; AND STUART, H. C.: Nutrition Studies During Pregnancy. IV. Relation of Protein Content of Mother's Diet During Pregnancy to Birth Length, Birth Weight and Condition of Infant at Birth. J. Pediat., 23, p. 506, 1943. BURKE, B. S., BEAL, V. A., KIRKWOOD, S. B., AND STUART, H. C.: The Influence of Nutrition During Pregnancy Upon the Condition of the Infant at Birth. J. Nutrition, 26, p. 569, 1943. EBBS, J. H., TISDALE, F. F., AND SCOTT, W. A.: The Influence of Prenatal Diet on the Mother and Child. J. Nutrition, 22, p. 515, 1941. SPIES, T. D., EWING, G. D., AND MANN, A. W.: Effect of Synthetic Niacin Amide, Synthetic Thiamine and Synthetic riboflavin on Infants and Young Children with Deficiency Diseases. Arch. of Pediat., 61, p. 517, 1944.



## ANNUAL MEETING

### ATLANTIC CITY, MARCH 11, 12, 13, 14, 15, 1946

The first post-war Federation meeting was planned to be held in Cleveland but when the ODT lifted the ban on convention travel the Local Committee found it impossible to secure requisite commitments. Efforts were then made to obtain facilities in New York, Chicago, Philadelphia, St. Louis and Baltimore. These failed. Arrangements were finally made for the meeting in Atlantic City under the sponsorship of a Philadelphia Local

Committee. The Local Committee regrets that the expense of attending the meeting must be somewhat higher than heretofore and that the only available time is that indicated above.

Provisional arrangements for the meeting by the Local Committee are given below. Final arrangements will be published in the program section of the next issue.

### ATLANTIC CITY MEETING

The Federation will meet in Atlantic City March 11, 12, 13, 14, 15, 1946. Scientific and business meetings will be held Tuesday, Wednesday, Thursday and Friday. Monday will be devoted to Council and Executive Committee meetings and to registration.

All of the functions will be centralized in the Municipal Convention Hall. This includes Federation headquarters, registration, Joint Session, section meetings, symposia, motion picture demonstrations and smokers. No facilities for static demonstrations can be supplied. Programs and additional announcements will appear in the March issue of *Federation Proceedings*.

*Registration* will open at 9 A.M. on Monday, March 11, at the Convention Hall. Members of any of the constituent societies and interested physicians, students or workers in biological laboratories may register. A registration fee of \$2.00 will be required. Admittance to the scientific sessions will be restricted to those who have registered. Programs, preprints and tickets to smokers and special functions will be on sale at the registration counter.

*Hotel reservations* are to be made through the Atlantic City Housing Bureau by the individuals themselves. Blanks for this purpose are being distributed through the secretaries of the constituent societies and should be filled out and transmitted at the earliest time practicable. The Atlantic City hotels were occupied by the Army when ceiling rates were installed elsewhere and their scheduled rates now are relatively high. However the price per person can be kept down by having four persons occupy two room suites, of which a considerable number are available. The Local Committee have been promised the full cooperation of the Housing Bureau in securing the largest possible number of rooms at the lower end of the rate sche-

dules. It is important that the first, second and third choices be indicated in applying for hotel accommodations.

*Motion Pictures.* Only 16 mm. safety film can be shown. Equipment for sound projection will be available. Each film can be shown several times and a schedule prepared by the Local Committee will be available at the time of the meeting. It is desirable that someone familiar with the film be on hand to explain it when it is projected. The Secretary of the Local Committee must be notified before February 15, 1946 as to the title, authorship, size of reel and time of run. Motion pictures cannot be shown at the scientific sessions and only those officially listed on the program will be projected.

*Informal smokers* are planned for Tuesday and Thursday evenings.

*Local Committee.* This represents the five Philadelphia medical schools, which conjointly are sponsoring the Atlantic City meeting.

A. N. Richards (Pennsylvania), chairman; C. F. Schmidt (Pennsylvania) secretary; Marion Fay (Woman's); A. Cantarow (Jefferson); A. E. Livingston (Temple); J. C. Scott (Hahnemann).

Communications relative to the program and arrangements for the scientific meetings should be addressed to Dr. C. F. Schmidt, University of Pennsylvania School of Medicine, Philadelphia 4, Pa. Inquiries about hotels, special luncheons and dinners and other similar functions should be sent directly to Mr. A. H. Skean, Manager Convention Bureau, 16 Central Pier, Atlantic City, N. J.

The five medical schools in Philadelphia cordially invite their visiting colleagues to arrange to visit them when passing through Philadelphia en route to or from the meetings. Monday, March 11, and Saturday, March 16, are suggested as convenient days for this purpose.

## EXECUTIVE COMMITTEE, 1946

PHILIP BARD, WALLACE O. FENN, The Physiological Society  
BAIRD HASTINGS, ARNOLD K. BALLS, The Biochemical Society

ERWIN E. NELSON, RAYMOND N. BIETER, The Pharmacological Society

BALDUIN LUCKÉ, H. P. SMITH, The Pathological Society

WILLIAM C. ROSE, H. E. CARTER, The Institute of Nutrition

JACQUES J. BRONFENBRENNER, ARTHUR F. COCA, The Association of Immunologists

PHILIP BARD, *Chairman*, Johns Hopkins Medical School, Baltimore 5, Md.

ALBERT G. HOGAN, *Ex-Chairman*

D. R. HOOKER, *Secretary*, 19 W. Chase St., Baltimore 1, Md.

## STANDING COMMITTEES

*Defence of Biological Research*: ELLIOTT C. CUTTER, *Chairman*; GEORGE H. WHIPPLE, *Acting Chairman*; A. B. LUCKHARDT, C. I. REED.

*International Congresses*: H. S. GASSER, Physiology, *Chairman*; A. J. CARLSON, Physiology; D. D. VAN SLYKE, Biochemistry; E. K. MARSHALL, JR., Pharmacology; PEYTON ROUS, Pathology; L. A. MAYNARD, Nutrition; J. J. BRONFENBRENNER, Immunology.

*Public Information*: D. W. BRONK, *Chairman*; HARRY GOLDBLATT, R. G. HOSKINS.

*Placement Service*: H. B. LEWIS, *Director*.

*Representatives, Council A.A.A.S.*: G. PHILIP GRAEBFIELD, CHARLES G. KING.

*Federation Proceedings, Control Committee*: PHILIP BARD, *Chairman*; C. G. KING, ARTHUR P. LOCKE, MORTON McCUTCHEON, C. F. SCHMIDT, A. H. SMITH.

## FORMER EXECUTIVE COMMITTEES

Philadelphia, Dec. 28-31, 1913

S. J. MELTZER, *Chairman*, and A. J. CARLSON, *Secretary*, The Physiological Society. A. B. MACCALLUM and P. A. SHAFFER, The Biochemical Society. T. SOLLmann and J. AUER, The Pharmacological Society.

St. Louis, Dec. 27-30, 1914

G. LUSK, *Chairman*, and P. A. SHAFFER, *Secretary*, The Biochemical Society. T. SOLLMAN and J. AUER, The Pharmacological Society. R. M. PEARCE and G. H. WHIPPLE, The Pathological Society. W. B. CANNON and A. J. CARLSON, The Physiological Society.

Boston, Dec. 26-29, 1915

TORALD SOLLmann, *Chairman*, and JOHN AUER, *Secretary*, The Pharmacological Society. THEO-

BALD SMITH and PEYTON ROUS, The Pathological Society. W. B. CANNON and C. W. GREENE, The Physiological Society. WALTER JONES and P. A. SHAFFER, The Biochemical Society.

New York, Dec. 27-30, 1916

SIMON FLEXNER, *Chairman*, and PEYTON ROUS, *Secretary*, The Pathological Society. W. B. CANNON and C. W. GREENE, The Physiological Society. WALTER JONES and STANLEY R. BENEDICT, The Biochemical Society. REID HUNT and J. AUER, The Pharmacological Society.

Minneapolis-Rochester, Dec. 27-29, 1917

FREDERIC S. LEE, *Chairman*, and CHARLES W. GREENE, *Secretary*, The Physiological Society. CARL L. ALSBERG and STANLEY R. BENEDICT, The Biochemical Society. REID HUNT and L. G. ROWNTREE, The Pharmacological Society. LUDVIG HEKTOEN and HOWARD T. KARSNER, The Pathological Society.

Baltimore, April 24-26, 1918

CARL L. ALSBERG, *Chairman*, and STANLEY R. BENEDICT, *Secretary*, The Biochemical Society. REID HUNT and E. D. BROWN, The Pharmacological Society. H. GIDEON WELLS and HOWARD T. KARSNER, The Pathological Society. FREDERIC S. LEE and CHARLES W. GREENE, The Physiological Society.

Cincinnati, Dec. 29-31, 1919

A. S. LOEVENHART, *Chairman*, and E. D. BROWN, *Secretary*, The Pharmacological Society. W. G. MACCALLUM and HOWARD T. KARSNER, The Pathological Society. WARREN P. LOMBARD and CHARLES W. GREENE, The Physiological Society. STANLEY R. BENEDICT and VICTOR C. MYERS, The Biochemical Society.

Chicago, Dec. 28-30, 1920

WILLIAM H. PARK, *Chairman*, and HOWARD T. KARSNER, *Secretary*, The Pathological Society. WARREN P. LOMBARD and CHARLES W. GREENE, The Physiological Society. STANLEY R. BENEDICT and VICTOR C. MYERS, The Biochemical Society. A. S. LOEVENHART and EDGAR D. BROWN, The Pharmacological Society.

New Haven, Dec. 28-30, 1921

J. J. R. MACLEOD, *Chairman*, and CHARLES W. GREENE, *Secretary*, The Physiological Society. D. D. VAN SLYKE and VICTOR C. MYERS, The Biochemical Society. C. W. EDMUND and EDGAR D. BROWN, The Pharmacological Society. F. G. NOVY and WADE H. BROWN, The Pathological Society.

Toronto, Dec. 27-29, 1922

D. D. VAN SLYKE, *Chairman*, and VICTOR C. MYERS, *Secretary*, The Biochemical Society. C. W. EDMUNDS and EDGAR D. BROWN, The Pharmacological Society. HOWARD T. KARSNER and WADE H. BROWN, The Pathological Society. J. J. R. MACLEOD and CHARLES W. GREENE, The Physiological Society.

St. Louis, Dec. 27-29, 1923

C. W. EDMUNDS, *Chairman*, and EDGAR D. BROWN, *Secretary*, The Pharmacological Society. E. L. ORIE and WADE H. BROWN, The Pathological Society. A. J. CARLSON and CHARLES W. GREENE, The Physiological Society. PHILIP A. SHAFFER and VICTOR C. MYERS, The Biochemical Society.

Washington, Dec. 29-31, 1924

ALDRED S. WARTHIN, *Chairman*, and E. B. KRUMBHAAR, *Secretary*, The Pathological Society. A. J. CARLSON and WALTER J. MEEK, The Physiological Society. P. A. SHAFFER and D. WRIGHT WILSON, The Biochemical Society. JOHN AUER and E. D. BROWN, The Pharmacological Society.

Cleveland, Dec. 28-30, 1925

A. J. CARLSON, *Chairman*, and WALTER J. MEEK, *Secretary*, The Physiological Society. H. C. SHERMAN and D. WRIGHT WILSON, The Biochemical Society. JOHN AUER and E. D. BROWN, The Pharmacological Society. GEORGE H. WHIPPLE and E. B. KRUMBHAAR, The Pathological Society.

Rochester, N. Y., April 14-16, 1927

E. C. KENDALL, *Chairman*, and F. C. KOCH, *Secretary*, The Biochemical Society. JOHN AUER and E. D. BROWN, The Pharmacological Society. W. H. BROWN and E. B. KRUMBHAAR, The Pathological Society. J. ERLANGER and W. J. MEEK, The Physiological Society.

Ann Arbor, April 12-14, 1928

CARL VOEGTLIN, *Chairman*, and E. D. BROWN, *Secretary*, The Pharmacological Society. DAVID MARINE and CARL V. WELLER, The Pathological Society. JOSEPH ERLANGER and WALTER J. MEEK, The Physiological Society. E. V. MCCOLLUM and D. WRIGHT WILSON, The Biochemical Society.

Boston, Aug. 19-24, 1929

(*The XIIIth International Physiological Congress*)

EDWARD B. KRUMBHAAR, *Chairman*, and CARL V. WELLER, *Secretary*, The Pathological Society. JOSEPH ERLANGER and WALTER J. MEEK, The Physiological Society. E. V. MCCOLLUM and D. WRIGHT WILSON, The Biochemical Society. CARL

VOEGTLIN and E. D. BROWN, The Pharmacological Society.

Chicago, March 26-29, 1930

WALTER J. MEEK, *Chairman*, and ALFRED C. REDFIELD, *Secretary*, The Physiological Society. W. R. BLOOR, and HOWARD B. LEWIS, The Biochemical Society. CARL VOEGTLIN and E. D. BROWN, The Pharmacological Society. WILLIAM F. PETERSEN and CARL V. WELLER, The Pathological Society.

Montreal, April 8-11, 1931

W. R. BLOOR, *Chairman*, and H. B. LEWIS, *Secretary*, The Biochemical Society. GEORGE B. WALLACE and E. D. BROWN, The Pharmacological Society. FREDERICK L. GATES and C. PHILLIP MILLER, The Pathological Society. WALTER J. MEEK and ARNO B. LUCKHARDT, The Physiological Society.

Philadelphia, April 27-30, 1932

GEORGE B. WALLACE, *Chairman*, and V. E. HENDERSON, *Secretary*, The Pharmacological Society. SAMUEL R. HAYTHORN and C. PHILLIP MILLER, The Pathological Society. WALTER J. MEEK and ARNO B. LUCKHARDT, The Physiological Society. H. C. BRADLEY and HOWARD B. LEWIS, The Biochemical Society.

Cincinnati, April 10-12, 1933

PEYTON ROUS, *Chairman*, and C. PHILLIP MILLER, *Secretary*, The Pathological Society. ARNO B. LUCKHARDT and FRANK C. MANN, The Physiological Society. H. C. BRADLEY and HOWARD B. LEWIS, The Biochemical Society. WM. DEB. MAGNIDER and V. E. HENDERSON, The Pharmacological Society.

New York, March 28-31, 1934

ARNO B. LUCKHARDT, *Chairman*, FRANK C. MANN, *Secretary*, and ALEXANDER FORBES, *Treasurer*, The Physiological Society. W. M. CLARK and H. A. MATTILL, The Biochemical Society. W. DEB. MAGNIDER and V. E. HENDERSON, The Pharmacological Society. CARL V. WELLER and C. PHILLIP MILLER, The Pathological Society.

Detroit, April 10-13, 1935

W. M. CLARK, *Chairman*, H. A. MATTILL, *Secretary*, and C. H. FISKE, *Treasurer*, the Biochemical Society. CHARLES W. GREENE and FRANK C. MANN, The Physiological Society. R. A. HATCHER and E. M. K. GEILING, The Pharmacological Society. S. BURT WOLBACH and SHIELDS WARREN, The Pathological Society.

Washington, March 25-28, 1936

V. E. HENDERSON, *Chairman*, E. M. K. GEILING, *Secretary*, and C. M. GRUBER, *Treasurer*, The

Pharmacological Society. FRANK C. MANN and ANDREW C. IVY, The Physiological Society. H. B. LEWIS and H. A. MATTILL, The Biochemical Society. OSKAR KLOTZ and SHIELDS WARREN, The Pathological Society.

Memphis, April 21-24, 1937

ALPHONSE R. DOCHEZ, *Chairman*, and SHIELDS WARREN, The Pathological Society. FRANK C. MANN and ANDREW C. IVY, The Physiological Society. HOWARD B. LEWIS and H. A. MATTILL, The Biochemical Society. V. E. HENDERSON and E. M. K. GEILING, The Pharmacological Society. D. R. HOOKER, *Secretary*.

Baltimore, March 30-April 2, 1938

WILLIAM T. PORTER, *Honorary President*; WALTER E. GARREY, *Chairman*, and ANDREW C. IVY, The Physiological Society. GLENN E. CULLEN and H. A. MATTILL, The Biochemical Society. ARTHUR L. TATUM and G. PHILIP GRABFIELD, The Pharmacological Society. C. PHILLIP MILLER and PAUL R. CANNON, The Pathological Society. D. R. HOOKER, *Secretary*.

Toronto, April 26-29, 1939

GLENN E. CULLEN, *Chairman*, and CHARLES G. KING, The Biochemical Society. ARTHUR L. TATUM and G. PHILIP GRABFIELD, The Pharmacological Society. C. PHILLIP MILLER and PAUL R. CANNON, The Pathological Society. WALTER E. GARREY and ANDREW C. IVY, The Physiological Society. D. R. HOOKER, *Secretary*.

New Orleans, March 13-16, 1940

E. M. K. GEILING, *Chairman*, and G. PHILIP GRABFIELD, The Pharmacological Society. ERNEST W. GOODPASTURE and PAUL R. CANNON, The Pathological Society. ANDREW C. IVY and PHILIP

BARD, The Physiological Society. WILLIAM C. ROSE and CHARLES G. KING, The Biochemical Society. D. R. HOOKER, *Secretary*.

Chicago, April 15-19, 1941

SHIELDS WARREN, *Chairman*, and H. P. SMITH, The Pathological Society. THORNE M. CARPENTER and L. A. MAYNARD, The Institute of Nutrition. ANDREW C. IVY and PHILIP BARD, The Physiological Society. WILLIAM C. ROSE and CHARLES G. KING, The Biochemical Society. E. M. K. GEILING and G. PHILIP GRABFIELD, The Pharmacological Society. D. R. HOOKER, *Secretary*.

Boston, March 31, April 1, 2, 3, 4, 1942

ALBERT G. HOGAN, *Chairman*, and ARTHUR H. SMITH, The Institute of Nutrition. PHILIP BARD and CARL J. WIGGERS, The Physiological Society. RUDOLPH J. ANDERSON and ARNOLD K. BALLS, The Biochemical Society. E. M. K. GEILING and R. N. BIETER, The Pharmacological Society. JESSE L. BOLLMAN and H. P. SMITH, The Pathological Society. SHIELDS WARREN, *Ex-Chairman*. D. R. HOOKER, *Secretary*.

1943, 1944, 1945: The meetings scheduled for Cleveland were cancelled because of war conditions

PHILIP BARD, *Chairman*, and WALLACE O. FENN, The Physiological Society. E. A. DOISET and ARNOLD K. BALLS, The Biochemical Society. E. K. MARSHALL, JR. and RAYMOND N. BIETER, The Pharmacological Society. BALDUIN LUCKÉ and H. P. SMITH, The Pathological Society. LEONARD A. MAYNARD and ARTHUR H. SMITH, The Institute of Nutrition. JACQUES J. BRONFENBRENNER and ARTHUR F. COCA, The Association of Immunologists.

## FEDERATION BY-LAWS

### BY-LAWS

*Adopted at the Washington Meeting, 1936 and amended at the Boston Meeting, 1942*

1. The Presidents and Secretaries of the Constituent Societies, the Chairman of the Executive Committee of the preceding year and the Federation Secretary shall form the Executive Committee of the Federation.

2. The Chairmanship of the Executive Committee shall be held in turn by the Presidents of the Constituent Societies, who shall succeed one another annually in the order of seniority of the Societies.

3. The Executive Committee shall appoint annually from the membership of the Federation

a secretary-treasurer, to be known as the Federation Secretary.

4. The Federation Secretary shall: (a) Keep the minutes of the Executive Committee and distribute copies to the Secretaries of the Constituent Societies. (b) Make arrangements for the Annual Meeting with the Local Committee, with the approval of the Executive Committee. (c) Print in convenient combined form and distribute to the membership of the Federation the programs of the Constituent Societies as received from their respective Secretaries. (d) Undertake such other duties, to be decided upon from time to time by the Executive Committee, as do not conflict with the complete autonomy of the Constituent Societies.

5. The Executive Committee shall control all monies in the hands of the Federation Secretary, who shall make an annual report to the Executive Committee for audit and approval. The expenses of the Federation Secretary, as authorized by the Executive Committee, shall be the first charge on such monies and if insufficient for the purpose the Executive Committee shall prorata such expenses to the Constituent Societies of the Federation in proportion to their respective memberships.

The Executive Committee may appropriate Federation monies annually for the uses of Local Committees and for the uses of other authorized Committees but in the latter cases an audit of expenditures shall be made and approved before such committees are discharged.

6. The Executive Committee shall determine the place of the Annual Meeting, and the time shall be determined by the Local Committee, preferably within the period of March fifteenth to May first.

7. The local Committee at the place of meeting of the Federation shall charge such fee for registration as may be approved by the Executive Committee. The monies thus collected shall be used to defray the expenses of the Local Committee and the remainder, after such expenses have been met, shall be turned over to the Federation Secretary.

8. The Executive Committee shall consider measures of advantage to the Federation as a whole. Any Constituent Society may refer similar measures to the Executive Committee. No action, however, shall be taken by the Executive Committee unless specifically authorized by all the Constituent Societies.

9. The Chairman of the Executive Committee may appoint committees when the purposes of such committees have been approved by all the Constituent Societies of the Federation. Such committees shall be appointed for a term of one year, but may be continued and their members reappointed. Such committees shall report in writing to the Executive Committee, which shall in turn report thereon to the Constituent Societies either for information or recommendation. The Secretaries of the Constituent Societies shall report the recommendations of their respective Societies to the Executive Committee for final action.

10. All individuals whose names appear on the program by invitation or introduction and those registering from any recognized biological laboratory may be enrolled as Associate Members of the Federation for that Annual Meeting. Such Asso-

ciate Members may enjoy all the privileges of the Annual Meeting except that of voting.

11. No person may present orally more than one paper during all of the scientific sessions of the Constituent Societies at the time of the Annual Meeting except upon invitation of the Executive Committee or a Council. Papers must be submitted to the Secretary of the Society of which the proposer is a member. The proposer may request transfer to another program, but this may only be done with the consent of the Secretary of the Society concerned. Any Secretary who regards any paper submitted to him as better suited to the program of another Society may arrange this transfer with the Secretary of the Society concerned, if it be possible. Such transfer shall be indicated on the program.

12. Abstracts not to exceed two hundred and fifty words in length, of papers approved for presentation at all of the scientific sessions of all the Constituent Societies at the Annual Meeting, shall receive publication in the *Federation Proceedings*.

13. A Control Committee, consisting of at least one representative of each Constituent Society as designated by the several Councils, shall have editorial control over the *Federation Proceedings* which shall be financed as required by an annual assessment of all the members of each Constituent Society.

14. The Control Committee shall have power to choose certain additional papers presented at the Annual Meetings and from other sources, including material heretofore published in the Federation Yearbook, for publication in the *Federation Proceedings*.

## PLACEMENT SERVICE

The Federation maintains a service to act as a medium of communication between persons seeking positions for teaching or research and institutions that wish to fill vacancies in these sciences.

The service does not undertake to recommend or to pass judgment upon applicants. It aims merely to serve as a clearing-house for such information as above stated and to bring into touch with one another candidates for positions and vacancies to be filled.

Persons, whether members of the Federation or not, and institutions desiring to avail themselves of the service, may receive such information as is available without cost to the applicant.

All communications should be addressed to Dr. H. B. Lewis, Director, University of Michigan, Ann Arbor, Mich.

## THE AMERICAN PHYSIOLOGICAL SOCIETY

Founded December 30, 1887; Incorporated June 2, 1923

## OFFICERS ELECTED 1942

*President*—PHILIP BARD, Johns Hopkins School of Medicine, Baltimore, Md.

*Secretary*—WALLACE O. FENN, University of Rochester, School of Medicine and Dentistry, Rochester, N. Y.

*Treasurer*—HALLOWELL DAVIS, Harvard University School of Medicine, Boston, Mass.

*Council*—PHILIP BARD, WALLACE O. FENN, HOLLOWELL DAVIS, CHARLES H. BEST, University of Toronto, Canada, MAURICE B. VISSCHER, University of Minnesota, Minneapolis, HIRAM E. ESSEX, Mayo Foundation, Rochester, Minn., W. F. HAMILTON, University of Georgia, Augusta.

*Board of Publication Trustees*—ANDREW C. IVY, Chairman (1943-46), HOMER W. SMITH (1944-47), FRANK C. MANN (1945-48).

*Representative on the Division of Biology and Agriculture of the National Research Council*—FRANCIS O. SCHMITT (1945-48).

*Representative on the Division of Medical Sciences of the National Research Council*—H. C. BAZETT (1944-1947).

*Historian*—WALTER J. MEEK.

## PAST OFFICERS

*Organization Meeting, December 30, 1887*

S. WEIR MITCHELL, President

H. N. MARTIN, Secretary

1888 H. P. BOWDITCH, President; H. N. MARTIN, Secretary-Treasurer; J. G. CURTIS, H. C. WOOD, H. SEWALL, Councilors. 1889 S. WEIR MITCHELL, President; H. N. MARTIN, Secretary-Treasurer; H. P. BOWDITCH, J. G. CURTIS, H. C. WOODS, Councilors. 1890 S. WEIR MITCHELL, President; H. N. MARTIN, Secretary-Treasurer; H. P. BOWDITCH, J. G. CURTIS, H. H. DONALDSON, Councilors. 1891 H. P. BOWDITCH, President; H. N. MARTIN, Secretary-Treasurer; R. H. CHITTENDEN, J. G. CURTIS, H. N. DONALDSON, Councilors. 1892 H. P. BOWDITCH, President; H. N. MARTIN, Secretary-Treasurer; R. H. CHITTENDEN, J. G. CURTIS, W. H. HOWELL, Councilors. 1893 H. P. BOWDITCH, President; W. P. LOMBARD, Secretary-Treasurer; R. H. CHITTENDEN, J. G. CURTIS, W. H. HOWELL, Councilors. 1894 H. P. BOWDITCH, President; W. P. LOMBARD, Secretary-Treasurer; R. H. CHITTENDEN, W. H. HOWELL, J. W. WARREN, Councilors. 1895 H. P. BOWDITCH, President; F. S. LEE, Secretary-Treasurer; R. H. CHITTENDEN, W. H. HOWELL, W. P. LOMBARD, Councilors. 1896 R. H. CHITTENDEN, President; F. S. LEE, Secretary-Treasurer; H. P. BOWDITCH, W. H. HOWELL, J. W. WARREN, Councilors. 1897 R. H. CHITTENDEN, President; F. S. LEE, Secre-

tary-Treasurer; H. P. BOWDITCH, W. H. HOWELL, W. P. LOMBARD, Councilors. 1898 R. H. CHITTENDEN, President; F. S. LEE, Secretary-Treasurer; H. P. BOWDITCH, W. H. HOWELL, W. P. LOMBARD, Councilors. 1899 R. H. CHITTENDEN, President; F. S. LEE, Secretary-Treasurer; W. H. HOWELL, W. P. LOMBARD, W. T. PORTER, Councilors. 1900 R. H. CHITTENDEN, President; F. S. LEE, Secretary-Treasurer; W. H. HOWELL, W. P. LOMBARD, W. T. PORTER, Councilors. 1901 R. H. CHITTENDEN, President; F. S. LEE, Secretary-Treasurer; W. H. HOWELL, W. P. LOMBARD, W. T. PORTER, Councilors. 1902 R. H. CHITTENDEN, President; F. S. LEE, Secretary-Treasurer; W. H. HOWELL, W. P. LOMBARD, W. T. PORTER, Councilors. 1903 R. H. CHITTENDEN, President; F. S. LEE, Secretary-Treasurer; W. H. HOWELL, W. P. LOMBARD, W. T. PORTER, Councilors. 1904 R. H. CHITTENDEN, President; W. T. PORTER, Secretary-Treasurer; F. S. LEE, W. P. LOMBARD, W. H. HOWELL, Councilors. 1905 W. H. HOWELL, President; L. B. MENDEL, Secretary; W. B. CANNON, Treasurer; R. H. CHITTENDEN, S. J. MELTZER, Councilors. 1906 W. H. HOWELL, President; L. B. MENDEL, Secretary; W. B. CANNON, Treasurer; A. B. MACALLUM, S. J. MELTZER, Councilors. 1907 W. H. HOWELL, President; L. B. MENDEL, Secretary; W. B. CANNON, Treasurer; J. J. ABEL, G. LUSK, Councilors. 1908 W. H. HOWELL, President; R. HUNT, Secretary; W. B. CANNON, Treasurer; J. J. ABEL, G. LUSK, Councilors. 1909 W. H. HOWELL, President; R. HUNT, Secretary; W. B. CANNON, Treasurer; A. J. CARLSON, W. P. LOMBARD, Councilors. 1910 W. H. HOWELL, President; A. J. CARLSON, Secretary; W. B. CANNON, Treasurer; J. ERLANGER, F. S. LEE, Councilors. 1911 S. J. MELTZER, President; A. J. CARLSON, Secretary; W. B. CANNON, Treasurer; J. ERLANGER, F. S. LEE, Councilors. 1912 S. J. MELTZER, President; A. J. CARLSON, Secretary; W. B. CANNON, Treasurer; J. ERLANGER, F. S. LEE, Councilors. 1913 S. J. MELTZER, President; A. J. CARLSON, Secretary; J. ERLANGER, Treasurer; W. B. CANNON, F. S. LEE, Councilors. 1914 W. B. CANNON, President; A. J. CARLSON, Secretary; J. ERLANGER, Treasurer; F. S. LEE, S. J. MELTZER, Councilors. 1915 W. B. CANNON, President; C. W. GREENE, Secretary; J. ERLANGER, Treasurer; W. E. GARREY, W. H. HOWELL, J. J. R. MACLEOD, W. J. MEEK, Councilors. 1916 W. B. CANNON, President; C. W. GREENE, Secretary; J. ERLANGER, Treasurer; W. E. GARREY, W. H. HOWELL, J. J. R. MACLEOD, W. J. MEEK, Councilors. 1917 F. S. LEE, President; C. W. GREENE, Secretary; J. ERLANGER, Treasurer; W. B. CANNON, W. H. HOWELL, J. J.

R. MACLEOD, W. J. MEEK, Councilors. 1918 F. S. LEE, President; C. W. GREENE, Secretary; J. ERLANGER, Treasurer; W. B. CANNON, W. H. HOWELL, J. J. R. MACLEOD, W. J. MEEK, Councilors. 1919 W. P. LOMBARD, President; C. W. GREENE, Secretary; J. ERLANGER, Treasurer; W. B. CANNON, Y. HENDERSON, J. J. R. MACLEOD, W. J. MEEK, Councilors. 1920 W. P. LOMMARD, President; C. W. GREENE, Secretary; J. ERLANGER, Treasurer; W. B. CANNON, J. J. R. MACLEOD, Y. HENDERSON, C. J. WIGGERS, Councilors. 1921 J. J. R. MACLEOD, President, C. W. GREENE, Secretary; J. ERLANGER, Treasurer; J. A. E. EYSTER, Y. HENDERSON, C. J. WIGGERS, A. J. CARLSON, Councilors. 1922 J. J. R. MACLEOD, President; C. W. GREENE, Secretary; J. ERLANGER, Treasurer; A. J. CARLSON, President; C. J. WIGGERS, A. J. CARLSON, J. A. E. EYSTER, Councilors. 1923 A. J. CARLSON, President; C. W. GREENE, Secretary; J. ERLANGER, Treasurer; C. J. WIGGERS, A. B. LUCKHARDT, J. A. E. EYSTER, J. R. MURLIN, Councilors. 1924 A. J. CARLSON, President; W. J. MEEK, Secretary; C. K. DRINKER, Treasurer; A. B. LUCKHARDT, J. A. E. EYSTER, J. R. MURLIN, W. E. GARREY, Councilors. 1925 A. J. CARLSON, President; W. J. MEEK, Secretary; C. K. DRINKER, Treasurer; J. A. E. EYSTER, J. R. MURLIN, W. E. GARREY, JOSEPH ERLANGER, Councilors. 1926 J. ERLANGER, President; W. J. MEEK, Secretary; A. FORBES, Treasurer; J. R. MURLIN, W. E. GARREY, A. B. LUCKHARDT, C. J. WIGGERS, Councilors. 1927 J. ERLANGER, President; W. J. MEEK, Secretary; A. FORBES, Treasurer; W. E. GARREY, A. B. LUCKHARDT, C. J. WIGGERS, R. GESELL, Councilors. 1928 J. ERLANGER, President; W. J. MEEK, Secretary; A. FORBES, Treasurer; A. B. LUCKHARDT, C. J. WIGGERS, R. GESELL, A. J. CARLSON, Councilors. 1929 W. J. MEEK, President; ALFRED C. REDFIELD, Secretary; A. FORBES, Treasurer; C. J. WIGGERS, R. GESELL, A. J. CARLSON, J. R. MURLIN, Councilors. 1930 W. J. MEEK, President; ARNO B. LUCKHARDT, Secretary; A. FORBES, Treasurer; R. GESELL, A. J. CARLSON, J. R. MURLIN, E. G. MARTIN, Councilors. 1931 W. J. MEEK, President; ARNO B. LUCKHARDT, Secretary; ALEXANDER FORBES, Treasurer; A. J. CARLSON, J. R. MURLIN, E. G. MARTIN, JOHN TAIT, Councilors. 1932 ARNO B. LUCKHARDT, President; FRANK C. MANN, Secretary; ALEXANDER FORBES, Treasurer; E. G. MARTIN, W. J. MEEK, J. R. MURLIN, JOHN TAIT, Councilors. 1933 ARNO B. LUCKHARDT, President; FRANK C. MANN, Secretary; ALEXANDER FORBES, Treasurer; HERBERT S. GASSER, ERNEST G. MARTIN, W. J. MEEK, JOHN TAIT, Councilors. 1934 CHARLES W. GREENE, President; FRANK C. MANN, Secretary; ALEXANDER FORBES, Treasurer; HERBERT S. GASSER, ARNO B. LUCKHARDT, W. J. MEEK, JOHN TAIT, Councilors. 1935 FRANK C. MANN, President; ANDREW C. IVY, Secretary; ALEXANDER FORBES, Treasurer; CHARLES H. BEST, HERBERT S. GASSER, ARNO B. LUCKHARDT, W. J. MEEK, Councilors. 1936 FRANK C. MANN President; ANDREW C. IVY, Secretary; WALLACE O. FENN, Treasurer; CHARLES H. BEST, PHILIP BARD, HERBERT S. GASSER, ARNO B. LUCKHARDT, Councilors. 1937 WALTER E. GARREY, President; ANDREW C. IVY, Secretary; WALLACE O. FENN, Treasurer; CHARLES H. BEST, PHILIP BARD, HERBERT S. GASSER, ARNO B. LUCKHARDT, Councilors. 1938 WILLIAM T. PONTER, Honorary President; WALTER E. GARREY, President; ANDREW C. IVY, Secretary; WALLACE O. FENN, Treasurer; ARNO B. LUCKHARDT, CHARLES H. BEST, PHILIP BARD, HERBERT S. GASSER, Councilors. 1939 ANDREW C. IVY, President; PHILIP BARD, Secretary; WALLACE O. FENN, Treasurer; CHARLES H. BEST, HERBERT S. GASSER, ARNO B. LUCKHARDT, MAURICE B. VISSCHER, Councilors. 1940 ANDREW C. IVY, President; PHILIP BARD, Secretary; CARL J. WIGGERS, Treasurer; CHARLES H. BEST, HERBERT S. GASSER, ARNO B. LUCKHARDT, MAURICE B. VISSCHER, Councilors. 1941 PHILIP BARD, President; CARL J. WIGGERS, Secretary; HALLOWELL DAVIS, Treasurer; CHARLES H. BEST, ARNO B. LUCKHARDT, MAURICE B. VISSCHER, HIRAM E. ESSEX, Councilors. 1942, 1943, 1944 PHILIP BARD, President; WALLACE O. FENN, Secretary; HALLOWELL DAVIS, Treasurer; CHARLES H. BEST, MAURICE B. VISSCHER, HIRAM E. ESSEX, W. F. HAMILTON, Councilors.

## CONSTITUTION

## I

1. This Society shall be named "THE AMERICAN PHYSIOLOGICAL SOCIETY."

2. The Society is instituted to promote the advance of Physiology and to facilitate personal intercourse between American Physiologists.

## II

1. The Society shall consist of ordinary and of honorary members.

2. Any person who has conducted and published original researches in Physiology, and who is a resident of North America, shall be eligible for election as an ordinary member of the Society.

3. Distinguished men of science who have contributed to the advance of Physiology shall be eligible for election as honorary members of the Society. Honorary members shall pay no membership fee. They shall have the right of attending the meetings of the Society, and of taking part in its scientific discussions, but they shall have no vote.

## III

1. The management of the Society shall be vested in a Council consisting of the President, Secretary, Treasurer, and four other members to be chosen from the ordinary members by ballot at each annual meeting. The President, Secretary, and Treasurer shall be elected for one year. The President shall be subject to only one re-election. The four additional members of the Council shall be elected for a term of four years, and the term of office of one of these councilors shall expire at the close of each annual meeting. He or she shall not be eligible for re-election for a period of two years.

2. The Council shall have power to fill such vacancies as may occur in its membership or in any committee of the Society unless the vacancy is produced by a resignation presented at a meeting.

## IV

1. At least a fortnight before the annual meeting the Secretary shall send to each member a notice of the place and time of each meeting, and shall make such other announcements as the Council shall direct.

2. The annual assessment shall be determined by the Council, and shall be due in advance at the time of the annual meeting. Beyond the ordinary expenditures required by the duties of the Secretary and Treasurer, no money of the Society shall be disbursed save by authority of the Council.

3. Any member whose assessment is two years in arrears shall cease to be a member of the Society, unless at the next annual meeting he shall be reinstated by special vote of the Society; and it shall be the duty of the Treasurer to inform the Secretary that he may notify the said delinquent of his right to appeal to said meeting.

4. Any member who has paid the annual assessment for thirty years, or who has attained the age of sixty-five years, or who has retired because of illness, may be relieved from the payment of the annual assessment.

## V

1. The annual meeting of the Society shall be held at a time and place determined by the Council in consultation with the Executive Committee of the Federation of American Societies for Experimental Biology.

2. Special meetings may be held at such times and places as the Council may determine.

## VI

1. Proposed changes in the Constitution must be sent in writing to the Secretary at least one month before the date of the meeting at which they are

to be considered, and must be signed by at least three ordinary members. The Secretary shall send a printed copy of any proposed change to each ordinary member at least two weeks before the next meeting.

2. If at this meeting two-thirds of the votes cast shall favor the proposed change, it shall be made.

3. At all annual meetings of the Society ten ordinary members shall form a quorum for the transaction of business.

## VII

1. The Council may, from the names of the candidates proposed in writing by at least two ordinary members of the Society, nominate candidates for election to ordinary membership. The names of the candidates so nominated, together with the names of their proposers and a statement of their qualifications for membership, shall be posted on a bulletin board at an annual meeting of the Society. The candidates may be balloted for at any session of the same meeting, and one black ball in eight shall exclude.

2. Honorary members shall be proposed by the Council, and shall be elected by ballot of the members present at an annual meeting and one negative vote in twenty shall exclude.

## VIII

If a majority of the Council shall decide that the interests of the Society require the expulsion of a member, the Secretary shall send a notice of this decision to each ordinary member at least two weeks before the next annual meeting. At this meeting the Secretary shall, on behalf of the Council, propose the expulsion; and if two-thirds of the members present vote for it, the member shall be expelled, his assessment for the current year shall be returned to him, and he shall cease to be a member of the Society.

## IX

1. The official organs of the Society shall be the *American Journal of Physiology* and such other Journals as the Society shall from time to time establish. These the Society shall own and manage.

2. The management of the Journals shall be vested in the Council. The Council shall make a full report to the Society at each annual meeting of the financial condition and the publication policy of the Journals.

## BY-LAWS

1. All papers read before the Society shall be limited to a length of ten minutes. No person may orally present more than one paper. In case of joint authorship the name of the individual who

will orally present the paper shall stand first.

2. Abstracts in duplicate, not to exceed two-hundred and fifty words in length, of all papers to be presented at the Annual Meeting of the Society shall be required by the Secretary for publication in the *Federation Proceedings*, in accordance with rules approved by the Council.

3. The Council may, upon the request of ten ordinary members, call a special meeting of the Society, at any time and place, for the reading of papers and the promotion of personal intercourse. Such meetings shall be held in accordance with the

Constitution and By-Laws of the Society; and if the regular officers of the Society are not present, the members in attendance shall elect a temporary Chairman and Secretary. The latter officer shall forward an account of the scientific proceedings of the meeting to the official Secretary of the Society for insertion in the minutes; he shall also prepare and transmit to the official Secretary such abstracts of papers read as may be furnished him, and these abstracts shall be published in the *Federation Proceedings* in accordance with By-Law 2.

## THE AMERICAN SOCIETY OF BIOLOGICAL CHEMISTS, INCORPORATED

*Founded December 6, 1906; Incorporated September 12, 1919*

### OFFICERS ELECTED 1945

*President*—A. B. HASTINGS, Harvard Medical School, Boston 15, Mass.

*Vice-President*—H. T. CLARKE, 630 W. 168th St., New York 32, N. Y.

*Secretary*—A. K. BALLS, U. S. Bureau of Agricultural and Industrial Chemistry, Western Regional Research Laboratory, Albany 6, California.

*Treasurer*—W. C. STADIE, Maloney Clinic, University of Pennsylvania, Philadelphia, Pa.

*Councilors-at-large*—R. J. ANDERSON, Sterling Laboratory, Yale University, New Haven, Conn.; C. F. CORI, Washington Univ. School of Medicine, St. Louis, Mo.; V. DU VIGNEAUD, Cornell University Medical College, New York City 21.

*Nominating Committee*—C. A. ELVEHJEM, Chairman, W. C. ROSE, E. A. EVANS, C. G. KING, D. D. VAN SLYKE, E. G. BALL, M. HEIDELBERGER, J. M. LUCK, R. R. WILLIAMS.

### PAST OFFICERS

1907 RUSSELL H. CHITTENDEN, President; J. J. ABEL, Vice-President; W. J. GIES, Secretary; L. B. MENDEL, Treasurer; W. JONES, W. KOCH, J. MARSHALL, T. B. OSBORNE, Councilors. 1908 JOHN J. ABEL, President; OTTO FOLIN, Vice-President; WM. J. GIES, Secretary; L. B. MENDEL, Treasurer; A. B. MACALLUM, A. P. MATHEWS, F. G. NOVY, Councilors. 1909 OTTO FOLIN, President; T. B. OSBORNE, Vice-President; WM. J. GIES, Secretary; L. B. MENDEL, Treasurer; J. J. ABEL, P. A. LEVENE, G. LUSK, Councilors. 1910 THOMAS B. OSBORNE, President; L. B. MENDEL, Vice-President; A. N. RICHARDS, Secretary; WALTER JONES, Treasurer; A. B. MACALLUM, A. P. MATHEWS, V. C. VAUGHAN, Councilors. 1911 LAFAYETTE B. MENDEL, President; A. B. MACALLUM, Vice-President; A. N. RICHARDS, Secretary; WALTER JONES, Treasurer; WM. J. GIES, A. S.

LOEVENHART, P. A. SHAFFER, Councilors. 1912 ARCHIBALD B. MACALLUM, President; G. LUSK, Vice-President; A. N. RICHARDS, Secretary; WALTER JONES, Treasurer; H. P. ARMSBY, L. B. MENDEL, H. G. WELLS, Councilors. 1913 ARCHIBALD B. MACALLUM, President; G. LUSK, Vice-President; P. A. SHAFFER, Secretary; D. D. VAN SLYKE, Treasurer; H. P. ARMSBY, L. B. MENDEL, H. G. WELLS, Councilors. 1914 GRAHAM LUSK, President; C. L. ALSBERG, Vice-President; P. A. SHAFFER, Secretary; D. D. VAN SLYKE, Treasurer; J. J. ABEL, A. B. MACALLUM, T. B. OSBORNE, Councilors. 1915 WALTER JONES, President; C. L. ALSBERG, Vice-President; P. A. SHAEFFER, Secretary; D. D. VAN SLYKE, Treasurer; OTTO FOLIN, G. LUSK, L. B. MENDEL, Councilors. 1916 WALTER JONES, President; F. P. UNDERHILL, Vice-President; S. R. BENEDICT, Secretary; D. D. VAN SLYKE, Treasurer; OTTO FOLIN, A. B. MACALLUM, P. A. SHAFFER, Councilors. 1917 CARL L. ALSBERG, President; A. P. MATHEWS, Vice-President; S. R. BENEDICT, Secretary; H. C. BRADLEY, Treasurer; L. J. HENDERSON, P. A. SHAFFER, F. P. UNDERHILL, Councilors. 1918 CARL L. ALSBERG, President; A. P. MATHEWS, Vice-President; S. R. BENEDICT, Secretary; H. C. BRADLEY, Treasurer; W. J. GIES, ANDREW HUNTER, E. V. McCOLLUM, Councilors. 1919 STANLEY R. BENEDICT, President; D. D. VAN SLYKE, Vice-President; V. C. MYERS, Secretary; H. C. BRADLEY, Treasurer; ANDREW HUNTER, E. V. McCOLLUM, L. B. MENDEL, Councilors. 1920 STANLEY R. BENEDICT, President; D. D. VAN SLYKE, Vice-President; V. C. MYERS, Secretary; H. C. BRADLEY, Treasurer; OTTO FOLIN, WALTER JONES, L. B. MENDEL, Councilors. 1921 DONALD D. VAN SLYKE, President; P. A. SHAFFER, Vice-President; V. C. MYERS, Secretary; H. C. BRADLEY, Treasurer; S. R. BENEDICT, OTTO FOLIN, WALTER JONES, Councilors. 1922 DONALD D. VAN SLYKE, President; P. A. SHAFFER, Vice-

President; V. C. MYERS, Secretary; W. R. BLOOR, Treasurer; S. R. BENEDICT, H. C. BRADLEY, A. P. MATHEWS, Councilors. 1923 PHILIP A. SHAFFER, President; H. C. SHERMAN, Vice-President; V. C. MYERS, Secretary; W. R. BLOOR, Treasurer; H. C. BRADLEY, ANDREW HUNTER, A. P. MATHEWS, Councilors. 1924 PHILIP A. SHAFFER, President; HENRY C. SHERMAN, Vice-President; D. WRIGHT WILSON, Secretary; WALTER R. BLOOR, Treasurer; OTTO FOLIN, ANDREW HUNTER, VICTOR C. MYERS, Councilors. 1925 HENRY C. SHERMAN, President; EDWARD C. KENDALL, Vice-President; D. WRIGHT WILSON, Secretary; WALTER R. BLOOR, Treasurer; OTTO FOLIN, LAFAYETTE B. MENDEL, PHILIP A. SHAFFER, Councilors. 1926 EDWARD C. KENDALL, President; ELMER V. MCCOLLUM, Vice-President; FRED C. KOCH, Secretary; GLENN E. CULLEN, Treasurer; J. B. COLLIP, EDWARD A. DOISY, ALBERT P. MATHEWS, Councilors. 1927 E. V. MCCOLLUM, President; W. R. BLOOR, Vice-President; D. WRIGHT WILSON, Secretary; G. E. CULLEN, Treasurer; E. A. DOISY, F. C. KOCH, D. D. VAN SLYKE, Councilors. 1928 E. V. MCCOLLUM, President; W. R. BLOOR, Vice-President; D. WRIGHT WILSON, Secretary; G. E. CULLEN, Treasurer; WM. M. CLARK, F. C. KOCH, D. D. VAN SLYKE, Councilors. 1929 W. R. BLOOR, President; H. C. BRADLEY, Vice-President; H. B. LEWIS, Secretary; G. E. CULLEN, Treasurer; W. M. CLARK, C. L. A. SCHMIDT, P. A. SHAFFER, Councilors. 1930 W. R. BLOOR, President; H. C. BRADLEY, Vice-President; H. B. LEWIS, Secretary; G. E. CULLEN, Treasurer; W. M. CLARK, P. A. SHAFFER, D. W. WILSON, Councilors. 1931 H. C. BRADLEY, President; W. M. CLARK, Vice-President; H. B. LEWIS, Secretary; C. H. FISKE, Treasurer; P. E. HOWE, W. C. ROSE, D. W. WILSON, Councilors. 1933 W. M. CLARK, President; H. B. LEWIS, Vice-President; H. A. MATTILL, Secretary; C. H. FISKE, Treasurer; H. C. BRADLEY, P. E. HOWE, W. C. ROSE, Councilors. 1934 W. M. CLARK, President; H. B. LEWIS, Vice-President; H. A. MATTILL, Secretary; C. H. FISKE, Treasurer; H. C. BRADLEY, P. E. HOWE, W. C. ROSE, D. W. WILSON, Councilors. 1935 H. B. LEWIS, President; G. E. CULLEN, Vice-President; H. A. MATTILL, Secretary; C. H. FISKE, Treasurer; H. C. BRADLEY, J. B. COLLIP, E. A. DOISY, Councilors. 1936 H. B. LEWIS, President; G. E. CULLEN, Vice-President; H. A. MATTILL, Secretary; A. B. HASTINGS, Treasurer; J. B. COLLIP, E. A. DOISY, W. C. ROSE, Councilors. 1937 G. E. CULLEN, President; W. C. ROSE, Vice-President; H. A. MATTILL, Secretary; A. B. HASTINGS, Treasurer; E. A. DOISY, H. B. LEWIS, H. B. VICKERY, Councilors. 1938 G. E.

CULLEN, President; W. C. ROSE, Vice-President; CHARLES G. KING, Secretary; A. B. HASTINGS, Treasurer; H. B. LEWIS, H. A. MATTILL, H. B. VICKERY, Councilors. 1939 W. C. ROSE, President; R. J. ANDERSON, Vice-President; CHARLES G. KING, Secretary; A. B. HASTINGS, Treasurer; H. B. LEWIS, H. A. MATTILL, G. E. CULLEN, Councilors. 1940 WILLIAM C. ROSE, President; RUDOLPH J. ANDERSON, Vice-President; CHARLES G. KING, Secretary; A. B. HASTINGS, Treasurer; H. A. MATTILL, GLENN E. CULLEN, E. A. DOISY, Councilors. 1941 R. J. ANDERSON, President; E. A. DOISY, Vice-President; A. K. BALLS, Secretary; W. C. STADIE, Treasurer; H. B. LEWIS, W. C. ROSE, Councilors. 1942 R. J. ANDERSON, President; E. A. DOISY, Vice-President; A. K. BALLS, Secretary; W. C. STADIE, Treasurer; W. C. ROSE, C. A. KING, H. Y. CLARKE, Councilors. 1943 E. A. DOISY, President; A. B. HASTINGS, Vice-President; A. K. BALLS, Secretary; W. C. STADIE, Treasurer; W. C. ROSE, H. T. CLARKE, R. J. ANDERSON, Councilors. 1944 E. A. DOISY, President; A. B. HASTINGS, Vice-President; A. K. BALLS, Secretary; W. C. STADIE, Treasurer; R. J. ANDERSON, H. T. CLARKE, V. DU VIGNEAUD, Councilors.

## CONSTITUTION

### FROM THE ARTICLES OF INCORPORATION

1. The name of the proposed corporation is "AMERICAN SOCIETY OF BIOLOGICAL CHEMISTS, INCORPORATED."
2. The purposes for which this corporation is formed are to further the extension of biochemical knowledge and to facilitate personal intercourse between American investigators in biological chemistry.

## BY-LAWS

### ARTICLE I.—Membership.

SECTION 1. *Eligibility for Membership.*—Qualified investigators who have conducted and published meritorious original investigations in biological chemistry shall be eligible for membership in the Society.

SEC. 2. *Nomination.*—Nominations for membership shall be made and seconded by members of the Society on blanks furnished by the Secretary. Nominations shall be submitted to the Council who shall determine eligibility and make recommendation to the Society at a regular meeting.

SEC. 3. *Election to Membership.*—A. A nominee for membership may be voted for by ballot at any meeting of the Society after Council has reported its findings on his eligibility. The eligible candidate shall be reported by the Council as "eligible" or as "eligible and indorsed." B. A majority of the ballots cast shall elect.

**SEC. 4. Forfeiture.**—A. Any member who may grant the use of his name for (a) the advertisement of a patent medicine, a proprietary food preparation, or any other commercial article of doubtful value to the public or possibly harmful to the public health, or (b) who may concede its use for the purpose of encouraging the sale of individual samples (of any such product) that he has not examined, shall forfeit his membership.

B. The Council shall have authority to announce forfeiture of membership, provided that the copy of the charges, together with a written notice of a hearing thereon by the Council at a place and time specified in such notice, shall have been delivered to the member charged with violating the preceding section either personally or mailed to him at his last known address at least thirty days before the date of such hearing.

**SEC. 5. Expulsion.**—Upon the recommendation of the Council any member may be expelled by a majority vote of the total membership at a meeting of the Society, provided that a copy of the charges against him, together with a written notice of a hearing thereon by the Council at a place and time specified in such notice shall have been delivered to him personally or mailed to him at his last known address at least thirty days before the date of such hearing.

#### ARTICLE II.—Meetings and Quorum

**SECTION 1. Annual.**—The annual meeting of the Society shall be held on the date fixed by the Certificate of Incorporation.

**SEC. 2. Special.**—A special meeting may be called at any time by the President, or in case of his absence or disability, by the Vice-President, and must be called at the request of a majority of the Council or fifteen members of the Society. A notice specifying the purpose of such meeting shall be mailed to each member at least ten days previous thereto. The Council shall select the places at which meetings shall be held.

**SEC. 3. Quorum.**—Fifteen members shall constitute a quorum at all meetings of the Society, but in absence of a quorum any number shall be sufficient to adjourn to a fixed date.

#### ARTICLE III.—Officials

**SECTION 1. Officers.**—The officers shall be a President, a Vice-President, a Secretary, and a Treasurer, who shall be elected annually by the members of the Society.

**SEC. 2. Council.**—A. The officers so elected and three additional members, one of whom shall be elected at each annual meeting of the Society to serve a three year term, shall constitute the Board of Directors of the corporation and shall be known as "The Council." (When this provision is first put into effect three members will need to be

elected for a one, a two and a three year period.)

B. No two members of the Council may be from the same institution, and none of the officers so elected shall be eligible for re-election for more than two years except the Secretary and Treasurer, who shall be eligible for re-election for five years. The three additional members of the Council shall be ineligible for re-election (until after the lapse of one year).

**SEC. 3. Duties of Officers.**—The powers and duties of the officers elected by the Society shall be such as usually devolve upon their respective positions.

**SEC. 4. Assistant Treasurer.**—A. The Council may from time to time appoint a trust company, or some member of the Society, to serve during the pleasure of the Council as Assistant Treasurer, and to act as depositary of the investments and income of the "Christian A. Herter Memorial Fund" and of such other funds as the Society may from time to time commit to its or his charge.

B. The Assistant Treasurer shall have and exercise the following powers and duties, viz., the custody and safe-keeping of securities and cash belonging to the "Christian A. Herter Fund" and the collection of income and other moneys due to the Fund, with power to receipt for the same and to endorse for deposit all checks payable to the Society or the Treasurer, or to the Journal of Biological Chemistry for income or other moneys due to the Fund, the investment or reinvestment of the capital of the Fund, subject to the approval of the Council; the disbursement of principal under the direction of the Council and the disbursement of income under the direction of the Editorial Board of the Journal of Biological Chemistry, such disbursement to be made under a resolution of the Council or Board, or with the approval of two members of either the Council or Board, as the case may be. The Assistant Treasurer shall keep books of account and render statements, annually or oftener upon the request of the Council or Board setting forth the condition of the Fund and the receipts and disbursements since the date of the preceding statement.

#### ARTICLE IV.—The Council

**SECTION 1. Powers.**—The general management of the Society during the intervals between meetings shall be vested in the Council, which shall regularly perform the ordinary duties of an executive committee and possess all the powers conferred upon the Board of Directors of a membership corporation by the Membership Corporation Law of the State of New York.

**SEC. 2. Reports.**—The Council shall report to the Society as promptly as possible its findings on the eligibility of candidates for membership, and on all charges of a violation of these By-Laws.

**SEC. 3. Journal of Biological Chemistry.**—The

Council shall have power to appoint the persons to act as proxies for the Society at all meetings of the stockholders of the "Journal of Biological Chemistry" (a corporation) of which all the stock is owned by the Society, and also to designate the persons to be elected as Directors of such corporation.

**SEC. 4. Herter Fund.**—It shall be the duty of the Council to see that the "Christian A. Herter Memorial Fund" is administered in accordance with the terms of the Trust Agreement, dated May 16, 1911, executed by the Journal of Biological Chemistry and the donors of said Fund.

#### ARTICLE V.—*Nominating Committee*

**SECTION 1. Membership.**—A. The nominating Committee shall consist of nine members from nine different institutions elected at each annual meeting to serve for the ensuing year. Members who have served on the Nominating Committee for two consecutive years shall be ineligible for re-election until after the lapse of one year.

B. The member of the Nominating Committee who is elected to the Committee by the largest number of votes shall become Chairman and Secretary of the Committee.

**SEC. 2. Nomination of Officials.**—A. The Nominating Committee shall make at least one nomination for each of the four offices and for each of the three additional positions in the Council to be filled by vote of the members.

B. The nominations by the Nominating Committee must be transmitted to the Secretary at least one month before the annual meeting at which they are to be considered.

C. The Secretary shall send to every member, at least two weeks before the annual meeting, two copies of the list of nominees presented to him by the Nominating Committee and at the same time shall notify all the members that they may vote by proxy.

D. At the opening of the first executive session of the ensuing annual meeting the Secretary shall formally present the regular nominations for the Nominating Committee.

E. Additional nominations for the offices and for membership in the Council may be made by any member at the opening of the first executive session of any annual meeting.

F. Nominations for membership on the Nominating Committee shall be made by or for individual members, either in person or by proxy, and not otherwise, at the opening of the first executive session of any annual meeting.

**SEC. 3. Election of Officials.**—A. The Secretary shall receive and present to the tellers, appointed by the President to take charge of the election, all signed ballots forwarded by absent members. When such ballots are presented to the tellers the Secretary shall announce the names of the mem-

bers voting by proxy, and he shall record the same names in the minutes of the meeting.

B. All elective officials shall be selected by ballot at the close of the first executive session of each annual meeting.

C. A majority of the votes cast shall be necessary to elect an official.

D. Elective officials shall take office on July 1st following the annual meeting.

**SEC. 4. Filling of Vacancies.**—A. The Nominating Committee shall fill all vacancies in elective positions except such as may occur at a meeting of the Society.

B. The President of the Society shall fill all vacancies in appointive positions.

#### ARTICLE VI.—*Financial*

**SECTION 1. Dues.**—Annual assessments shall be determined by majority vote at the annual meetings, upon the recommendation of the Council, and shall be due January 15th in each year. Members who have reached the age of 65 years, or who have become incapacitated, may, by vote of the Council, be exempted from the payment of dues.

**SEC. 2. Expenditures.**—No expenditures from the general funds of the Society except those required in the performance of the ordinary official duties shall be made except by vote of the Society or the Council, but this section shall not apply to expenditures from the "Christian A. Herter Memorial Fund."

**SEC. 3. Privileges of Membership Begin with Payment of Dues.**—Candidates for membership, if elected, shall not be entitled to any of the privileges of membership, before they pay the dues of the fiscal year succeeding their election.

**SEC. 4. Penalty for Non-Payment of Dues.**—A. Members in arrears for dues for a period of three consecutive years shall thereupon forfeit their membership.

B. Delinquent members may be reinstated by the Council provided all indebtedness to the Society is liquidated.

**SEC. 5. Herter Fund.**—The "Christian A. Herter Memorial Fund" shall be held and invested separately from the general funds of the Society and the income thereof shall be expended under the direction of the Editorial Board exclusively for the maintenance and support of the Journal of Biological Chemistry, subject to the supervision and control of the Editorial Committee in accordance with the terms of the Trust Agreement mentioned in ARTICLE IV, SECTION 4, and the provisions of ARTICLE VII of the By-Laws.

#### ARTICLE VII.—*Journal of Biological Chemistry*

**SECTION 1. Editorial Committee.**—There shall be an Editorial Committee consisting of nine mem-

bers of the Society who shall be nominated by the Nominating Committee and elected by the Society in the same manner as officers. The nine members first elected shall divide themselves by lot into three classes of three in each class, to serve for two, four, and six years respectively, and thereafter three members shall be elected at each alternate annual meeting of the Society to succeed the members of the outgoing class and to serve for a term of six years. Members of the Committee shall be eligible to re-election.

**Sec. 2. Powers of Committee.**—The Committee shall have power to elect an Editorial Board and shall have final authority in matters pertaining to the general policy of the Journal.

**Sec. 3. Editorial Board.**—The members of the Board shall hold office until their successors are elected and shall appoint a Managing Editor from among their own number who shall have direct responsibility and authority for the active editorial conduct of the Journal, and who shall have discretionary power in arranging the details as to the conduct of the Journal. The expenditures of the income of the "Christian A. Herter Memorial Fund" shall be under the direction of the Board, and the approval of any two members of the Board shall be a sufficient warrant to authorize payments from such income.

#### ARTICLE VIII.—Papers on Scientific Subjects

**SECTION 1. Presentation of Papers.**—The Secretary shall request each member who signifies his intention of reading a paper at any session to specify the length of time which its presentation will require. The time thus specified shall be printed on the official program, and the presiding officer shall have no authority to extend it unless a majority of the members present signify their wish to the contrary. In the absence of any specification of time required not more than ten minutes shall be allotted for the reading of any one paper.

**Sec. 2. Number of Papers.**—No member shall be

permitted to present more than one paper, either alone or in collaboration, until every member shall have had the opportunity of presenting one paper.

#### ARTICLE IX.—Corporate Seal

**SECTION I.** The corporate seal of the corporation shall be a circle surrounded by the words, "AMERICAN SOCIETY OF BIOLOGICAL CHEMISTS," and including the word, "INCORPORATED."

#### ARTICLE X.—Amendments

**SECTION 1. Amendments.**—These By-Laws, after having been approved by the Council, and adopted by the Society at its first annual meeting, shall not be amended except as hereinafter provided.

**Sec. 2. Manner of Presentation.**—Proposed amendments to the By-Laws must be sent to the Secretary at least one month before the date of the meeting at which they are to be considered and must be indorsed in writing by at least three members.

**Sec. 3. Notice of Intended Amendments.**—The Secretary shall give every member notice of proposed amendments at least two weeks before the meeting at which they are to be considered and shall notify all members that they may vote by proxy.

**Sec. 4. Adoption of Amendments.**—A. The Secretary shall receive and present to the tellers appointed by the President all signed ballots forwarded by absent members. When such ballots are presented to the tellers, the Secretary shall announce the names of members voting by proxy, and he shall record the same names in the minutes of the meeting.

B. Votes upon amendments shall be cast at the opening of the second executive session of the meeting at which they are considered.

C. Affirmative votes from three-fifths of the members voting shall be required for the adoption of an amendment.

## AMERICAN SOCIETY FOR PHARMACOLOGY AND EXPERIMENTAL THERAPEUTICS, INCORPORATED

*Founded December 28, 1908; Incorporated June 19, 1938*

### OFFICERS ELECTED 1945

**President**—ERWIN E. NELSON, Wellcome Research Laboratories, Tuckahoe 7, New York.

**Vice-President**—CHARLES M. GRUBER, Jefferson Medical College, Philadelphia 7, Pennsylvania.

**Secretary**—RAYMOND N. BIETER, University of Minnesota Medical School, Minneapolis 14, Minnesota.

**Treasurer**—MCKEEN CATTELL, Cornell University Medical College, New York 21, New York.

**Council**—HARRY BECKMAN, Marquette University School of Medicine, Milwaukee 3, Wisconsin, NATHAN B. EDDY, National Institute of Health, Bethesda 14, Maryland, ERWIN E. NELSON, CHARLES M. GRUBER, RAYMOND N. BIETER, MCKEEN CATTELL.

**Membership Committee**—HARVEY B. HAAG (term expires 1946) Medical College of Virginia, Richmond 19, Va., CARL A. DRAGSTEDT (term expires 1947) Northwestern University Medical

School, Chicago 11, Ill., CARL F. SCHMIDT (term expires 1948), University of Pennsylvania Medical School, Philadelphia 4, Pennsylvania.

*Nominating Committee*—RALPH G. SMITH, Chairman, E. G. GROSS, A. E. LIVINGSTON, ROBERT P. WALTON, ARNOLD WELCH.

### PAST OFFICERS

1909 J. J. ABEL, President; REID HUNT, Secretary; A. S. LOEVENHART, Treasurer; S. J. MELTZER, T. SOLLMANN, C. W. EDMUNDS, A. C. CRAWFORD, Councilors. 1910 J. J. ABEL, President; REID HUNT, Secretary; A. S. LOEVENHART, Treasurer; A. C. CRAWFORD, G. B. WALLACE, Councilors. 1911 J. J. ABEL, President; REID HUNT, Secretary; A. S. LOEVENHART, Treasurer; G. B. WALLACE, W. DEB. MACNIDER, Councilors. 1912 J. J. ABEL, President; J. AUER, Secretary; A. S. LOEVENHART, Treasurer; G. B. WALLACE, REID HUNT, Councilors. 1913 T. SOLLMANN, President; J. AUER, Secretary; A. S. LOEVENHART, Treasurer; J. J. ABEL, W. DEB. MACNIDER, Councilors. 1914 T. SOLLMANN, President; J. AUER, Secretary; W. DEB. MACNIDER, Treasurer; J. J. ABEL, A. S. LOEVENHART, Councilors. 1915 T. SOLLMANN, President; J. AUER, Secretary; W. DEB. MACNIDER, Treasurer; WORTH HALE, D. E. JACKSON, Councilors. 1916 REID HUNT, President; J. AUER, Secretary; W. DEB. MACNIDER, Treasurer; A. D. HIRSCHFELDER, G. B. ROTH, Councilors. 1917 REID HUNT, President; L. G. ROWNTREE, Secretary; W. DEB. MACNIDER, Treasurer; J. AUER, CARL VOEGTLIN, Councilors. 1918 REID HUNT, President; E. D. BROWN, Secretary; W. DEB. MACNIDER, Treasurer; HUGH McGUIGAN, CARL VOEGTLIN, Councilors. 1919 A. S. LOEVENHART, President; E. D. BROWN, Secretary; W. DEB. MACNIDER, Treasurer; REID HUNT, E. K. MARSHALL, JR., Councilors. 1920 A. S. LOEVENHART, President; E. D. BROWN, Secretary; W. DEB. MACNIDER, Treasurer; D. E. JACKSON, E. K. MARSHALL, JR., Councilors. 1921 C. W. EDMUNDS, President; E. D. BROWN, Secretary; HUGH McGUIGAN, Treasurer; JOHN AUER, J. P. HANZLIK, Councilors. 1922 C. W. EDMUNDS, President; E. D. BROWN, Secretary; HUGH McGUIGAN, Treasurer; J. P. HANZLIK, H. G. BARBOUR, Councilors. 1923 C. W. EDMUNDS, President; E. D. BROWN, Secretary; HUGH McGUIGAN, Treasurer; J. P. HANZLIK, H. G. BARBOUR, Councilors. 1924 JOHN AUER, President; E. D. BROWN, Secretary; A. L. TATUM, Treasurer; J. P. HANZLIK, H. G. BARBOUR, Councilors. 1925 JOHN AUER, President; E. D. BROWN, Secretary; A. L. TATUM, Treasurer; H. G. BARBOUR, W. DEB. MACNIDER, Councilors. 1926 JOHN AUER, President; E. D. BROWN, Secretary; A. L. TATUM, Treasurer; H. G. BARBOUR, W. DEB. MACNIDER, Councilors. 1927 CARL

VOEGTLIN, President; E. D. BROWN, Secretary; A. L. TATUM, Treasurer; V. E. HENDERSON, C. W. EDMUNDS, Councilors. 1928 CARL VOEGTLIN, President; E. D. BROWN, Secretary; A. L. TATUM, Treasurer; V. E. HENDERSON, C. W. EDMUNDS, Councilors. 1929 CARL VOEGTLIN, President; E. D. BROWN, Secretary; O. H. PLANT, Treasurer; V. E. HENDERSON, C. W. EDMUNDS, Councilors. 1930 GEORGE B. WALLACE, President; E. D. BROWN, Secretary; O. H. PLANT, Treasurer; H. G. BARBOUR, C. M. GRUBER, Councilors. 1931 GEORGE B. WALLACE, President; VELYIEN E. HENDERSON, Secretary; O. H. PLANT, Treasurer; PAUL D. LAMSON, WILLIAM DEB. MACNIDER, Councilors. 1932 WM. DEB. MACNIDER, President; A. N. RICHARDS, Vice-President; V. E. HENDERSON, Secretary; O. H. PLANT, Treasurer; G. B. ROTH, A. L. TATUM, Councilors. 1933 WM. DEB. MACNIDER, President; A. L. TATUM, Vice-President; V. E. HENDERSON, Secretary; O. H. PLANT, Treasurer; C. M. GRUBER, G. B. ROTH, Councilors. 1934 R. A. HATCHER, President; A. L. TATUM, Vice-President; E. M. K. GEILING, Secretary; O. H. PLANT, Treasurer; WM. DEB. MACNIDER, R. L. STEHLE, Councilors. 1935 V. E. HENDERSON, President; O. H. PLANT, Vice-President; E. M. K. GEILING, Secretary; C. M. GRUBER, Treasurer; FLOYD DE EDs, M. S. DOOLEY, Councilors. 1936 V. E. HENDERSON, President; O. H. PLANT, Vice-President; E. M. K. GEILING, Secretary; C. M. GRUBER, Treasurer; C. W. EDMUNDS, G. B. WALLACE, Councilors. 1937 A. L. TATUM, President; F. M. K. GEILING, Vice-President; G. P. GRABFIELD, Secretary; C. M. GRUBER, Treasurer; V. E. HENDERSON, M. H. SEEVERS, Councilors. 1938 A. L. TATUM, President; E. M. K. GEILING, Vice-President; G. P. GRABFIELD, Secretary; C. M. GRUBER, Treasurer; E. K. MARSHALL, JR., C. F. SCHMIDT, Councilors. 1939 O. H. PLANT, President; E. M. K. GEILING, Vice-President; G. P. GRABFIELD, Secretary; E. E. NELSON, Treasurer; A. L. TATUM, C. A. DRAGSTEDT, Councilors. 1940 E. M. K. GEILING, President; C. F. SCHMIDT, Vice-President; G. PHILIP GRABFIELD, Secretary; E. E. NELSON, Treasurer; B. H. ROBBINS, C. H. THIENES, Councilors. 1941 E. M. K. GEILING, President; C. F. SCHMIDT, Vice-President; RAYMOND N. BIETER, Secretary; E. E. NELSON, Treasurer; E. G. GROSS, R. G. SMITH, Councilors. 1942 E. K. MARSHALL, JR., President; CARL A. DRAGSTEDT, Vice-President; RAYMOND N. BIETER, Secretary; E. E. NELSON, Treasurer; McK. CATTELL, R. G. SMITH, Councilors. 1943 E. K. MARSHALL, JR., President; CARL A. DRAGSTEDT, Vice-President; RAYMOND N. BIETER, Secretary; E. E. NELSON, Treasurer; C. M. GRUBER, Vice-President; R. N. BIETER, Secretary; MCKEEN

CATELL, Treasurer; HARRY BECKMAN, NATHAN B. EDDY, Councilors.

## CONSTITUTION

### ARTICLE I.—Name

The name of this organization shall be the "AMERICAN SOCIETY FOR PHARMACOLOGY AND EXPERIMENTAL THERAPEUTICS, INCORPORATED."

### ARTICLE II.—Objects

The purpose of this Society shall be to promote these branches of science and to facilitate personal intercourse between investigators who are actively engaged in research in these fields.

### ARTICLE III.—Membership

**SECTION 1.** Any person who has conducted and published a meritorious investigation in pharmacology or experimental therapeutics, and who is an active investigator in one of these fields, shall be eligible to membership, subject to the conditions of the other sections of Article III.

**SEC. 2.** A. Candidates for membership to this Society shall be proposed by two members who are not members of the Council. The names so proposed shall be sent to the Secretary at least three months prior to the Annual Meeting.

B. The Membership Committee shall investigate the qualifications of the candidates and report to the Council.

C. Candidates reported upon by the Membership Committee to the Council may be recommended for admission by the Council only provided they have been unanimously approved by both the Membership Committee and the Council.

D. The names of the candidates recommended for admission by the Council shall be posted by the Secretary not later than the day preceding the election for members.

E. The election of members shall be by individual ballot; one opposing vote in every eight cast shall be sufficient to exclude a candidate from membership.

#### *SEC. 3. Forfeiture of Membership.*

A. Any member whose assessment is three years in arrears shall cease to be a member of the Society, unless he shall be reinstated by a special vote of the Council; and it shall be the duty of the Treasurer to inform the Secretary that he may notify the said delinquent of his right to appeal to the Council.

B. If the Council shall decide that it is for the best interests of the Society that a member be expelled, the member shall be notified and given an opportunity of a hearing before the Council. Upon the recommendation of the Council the member then may be expelled by a three-fourths vote of those present at a regular meeting of the Society.

#### *SEC. 4. Honorary Members.*

A. Distinguished men of science who have contributed to the advance of pharmacology or experimental therapeutics shall be eligible for election as honorary members of the Society.

B. Nominations for honorary members shall take the same course as nominations for ordinary members (Art. III, Sec. 2); but their election shall require the unanimous vote of the members present at the election.

C. Honorary members shall pay no membership fee. They shall have the right to attend all meetings of the Society, and to take part in its discussions, but they shall have no vote.

D. The conditions for continuation of membership shall be the same for honorary as for ordinary members (Art. III, Sec. 3), except that forfeiture for arrears of fees does not apply to honorary members.

### ARTICLE IV.—Officers and Elections

**SECTION 1.** The management of the Society shall be vested in a Council of six officers, consisting of a President, a Vice-President, a Secretary, a Treasurer, and two additional members.

**SEC. 2.** There shall be a Membership Committee consisting of three members, and a Nominating Committee consisting of five members. No two members of either Committee shall be from the same institution.

**SEC. 3.** Members of the Council shall serve for one year but they shall be eligible for re-election.

**SEC. 4.** The election of the Membership Committee shall be held annually at the time when the election of officers occurs. At the first meeting of the Society under this Constitution, one member shall be elected to serve on the Committee for three years, one for two years, and one for one year; and subsequently one member shall be elected each year to serve for a period of three years.

**SEC. 5.** A. Members of the Nominating Committee shall serve for one year. They are eligible for re-election, but shall not hold membership in the Committee for more than two consecutive years.

B. The Nominating Committee shall make at least one nomination for each office and for position on the Membership Committee to be filled by vote of the members. The nominations so made shall be transmitted to the Secretary and by him in turn to the members, at least one month before the annual meeting. Additional nominations may be made by any member at the time of the annual meeting.

C. Nominations for membership on the Nominating Committee shall be made by individual members at the time of the annual election. The five nominees who receive the highest number of votes shall be declared elected. The Nominating

Committee shall select its own chairman who shall also serve as secretary to the Committee.

SEC. 6. The election of officers shall be held at the close of the first session of the annual meeting. In voting there shall be a ballot in regular order for each office to be filled, and the majority of the votes cast shall be necessary to a choice.

SEC. 7. Such vacancies as may occur in the offices and in the various committees in the interval between annual meetings shall be filled by a majority vote of the Council.

#### ARTICLE V.—Meetings

SECTION 1. The annual meeting of the Society shall be held at a time and place determined by the Council in consultation with the Executive Committee of the Federation of American Societies for Experimental Biology.

SEC. 2. Special meetings may be held at such times and places as the Council may determine.

SEC. 3. At least four weeks before the annual meeting the Secretary shall send to each member a notice of the time and place of such meeting and shall make such announcements as the Council may direct.

#### ARTICLE VI.—Financial

SECTION 1. The annual assessment shall be determined by majority vote at the annual meetings, upon the recommendation of the Council, and shall be due in advance at the time of the meeting.

SEC. 2. Beyond the ordinary expenditures required by the routine business of the Society no money shall be disbursed save by the authority of the Council or Society.

SEC. 3. The treasurer shall make an annual report to the Society.

SEC. 4. In case any profits result to the Society from the Journal of Pharmacology and Experimental Therapeutics at the end of the financial year, such profits shall be kept in a special account, after deducting any sums expended by the Society during the year for the conduct of the Journal, and shall be held subject to the order of the Council on recommendation of the Editorial Board.

#### ARTICLE VII.—Quorum

Ten members shall constitute a quorum for the transaction of business.

#### ARTICLE VIII.—*By-Laws*

By-Laws shall be adopted, altered or repealed at any meeting by two-thirds vote of the ballots cast.

#### ARTICLE IX.—*Amendments*

SECTION 1. Intended amendments to the Constitution shall be sent to the Secretary at least one month before the date of the meeting at which they are to be considered, and must be indorsed in writing by at least three members.

SEC. 2. The Secretary shall give all members due notice of proposed amendments.

SEC. 3. A four-fifths vote of the members present shall be required for the adoption of an amendment.

#### ARTICLE X.—*Journal*

SECTION 1. The official publication of the Society shall be the Journal of Pharmacology and Experimental Therapeutics.

SEC. 2. The Society shall elect an Editor-in-Chief for a term of three years and he with the approval of the Council shall appoint an Editorial Board of six members for a term of three years.

SEC. 3. The Editorial Board shall have direct authority and responsibility for the active editorial conduct of the Journal of Pharmacology and Experimental Therapeutics and shall have discretionary power in arranging details as to the conduct of the Journal.

#### BY-LAWS

1. Papers to be read shall be selected by the President and Secretary, who shall be empowered to arrange the program in their discretion. Papers not read shall appear on the program as read by title. No member shall be permitted to read or have read by title more than one paper.

2. An abstract of a paper to be read before the Society shall be sent to the Secretary with the title. As early as possible after each meeting, the Secretary shall edit and publish the Proceedings of the Society together with abstracts in a publication authorized by the Society.

3. All applications for membership shall be accompanied by a copy of as many reprints as possible of the published work of the applicant.

## THE AMERICAN SOCIETY FOR EXPERIMENTAL PATHOLOGY

*Founded December 29, 1915*

## OFFICERS ELECTED 1942

*President*—BALDUIN LUCKÉ, University of Pennsylvania Medical School, Philadelphia.

*Vice-President*—PAUL R. CANNON, University of Chicago, Chicago, Illinois.

*Secretary-Treasurer*—H. P. SMITH, College of Physicians and Surgeons, Columbia University, New York, N. Y.

*Councilors*—DOUGLAS H. SPRUNT, University of Tennessee, Memphis; FRIEDA S. ROBSCHER-Robbins, University of Rochester School of Medicine and Dentistry, Rochester, N. Y.

## PAST OFFICERS

1914 R. M. PEARCE, President; JOHN F. ANDERSON, Vice-President; G. H. WHIPPLE, Secretary-Treasurer; HARVEY CUSHING, DAVID MARINE, Councilors. 1915 THEOBALD SMITH, President; G. H. WHIPPLE, Vice-President; PEYTON ROUS, Secretary-Treasurer; DAVID MARINE, R. M. PEARCE, Councilors. 1916 SIMON FLEXNER, President; LEO LOEB, Vice-President; PEYTON ROUS, Secretary-Treasurer; DAVID MARINE, R. M. PEARCE, Councilors. 1917 LUDVIG HEKTOEN, President; LEO LOEB, Vice-President; HOWARD T. KARSNER, Secretary-Treasurer; PAUL A. LEWIS, L. G. ROWNTREE, Councilors. 1918 H. GIDEON WELLS, President; W. G. MACCALLUM—Vice-President; HOWARD T. KARSNER, Secretary-Treasurer; L. G. ROWNTREE, LUDVIG HEKTOEN, Councilors. 1919 W. G. MACCALLUM, President; WILLIAM H. PARK, Vice-President; HOWARD T. KARSNER, Secretary-Treasurer; LUDVIG HEKTOEN, E. L. OPIE, Councilors. 1920 WILLIAM H. PARK, President; F. G. NOVY, Vice-President; HOWARD T. KARSNER, Secretary-Treasurer; E. L. OPIE, WADE H. BROWN, Councilors. 1921 F. G. NOVY, President; HOWARD T. KARSNER, Vice-President; WADE H. BROWN, Secretary-Treasurer; PAUL A. LEWIS, A. R. DOCHEZ, Councilors. 1922 HOWARD T. KARSNER, President; EUGENE L. OPIE, Vice-President; WADE H. BROWN, Secretary-Treasurer; A. R. DOCHEZ, GEORGE H. WHIPPLE, Councilors. 1923 EUGENE L. OPIE, President; ALDRED S. WARTHIN, Vice-President; WADE H. BROWN, Secretary-Treasurer; GEORGE H. WHIPPLE, H. GIDEON WELLS, Councilors. 1924 ALDRED S. WARTHIN, President; GEORGE H. WHIPPLE, Vice-President; EDWARD B. KRUMBHAAR, Secretary-Treasurer; H. GIDEON WELLS, FREDERICK L. GATES, Councilors. 1925 GEORGE H. WHIPPLE, President; WADE H. BROWN, Vice-President; EDWARD B. KRUMBHAAR, Secretary-Treasurer; FREDERICK L. GATES, DAVID MARINE, Councilors. 1926 WADE H. BROWN, President; DAVID MARINE,

Vice-President; EDWARD B. KRUMBHAAR, Secretary-Treasurer; FREDERICK L. GATES, WILLIAM F. PETERSEN, Councilors. 1927 DAVID MARINE, President; EDWARD B. KRUMBHAAR, Vice-President; CARL V. WELLER, Secretary-Treasurer; WILLIAM F. PETERSEN, FREDERICK L. GATES, Councilors. 1928 EDWARD B. KRUMBHAAR, President; WILLIAM F. PETERSEN, Vice-President; CARL V. WELLER, Secretary-Treasurer; FREDERICK L. GATES, SAMUEL R. HAYTHORN, Councilors. 1929 WILLIAM F. PETERSEN, President; FREDERICK L. GATES, Vice-President; CARL V. WELLER, Secretary-Treasurer; SAMUEL R. HAYTHORN, PEYTON ROUS, Councilors. 1930 FREDERICK L. GATES, President; SAMUEL R. HAYTHORN, Vice-President; C. PHILLIP MILLER, Secretary-Treasurer; PEYTON ROUS, CARL V. WELLER, Councilors. 1931 SAMUEL R. HAYTHORN, President; PEYTON ROUS, Vice-President; C. PHILLIP MILLER, Secretary-Treasurer; CARL V. WELLER, S. BURT WOLBACH, Councilors. 1932 PEYTON ROUS, President; CARL V. WELLER, Vice-President; C. PHILLIP MILLER, Secretary-Treasurer; S. BURT WOLBACH, OSKAR KLOTZ, Councilors. 1933 CARL V. WELLER, President; S. BURT WOLBACH, Vice-President; C. PHILLIP MILLER, Secretary-Treasurer; OSKAR KLOTZ, ALPHONSE R. DOCHEZ, Councilors. 1934 S. BURT WOLBACH, President; OSKAR KLOTZ, Vice-President; SHIELDS WARREN, Secretary-Treasurer; C. PHILLIP MILLER, ALPHONSE R. DOCHEZ, Councilors. 1935 OSKAR KLOTZ, President; ALPHONSE R. DOCHEZ, Vice-President; SHIELDS WARREN, Secretary-Treasurer; MORTON McCUTCHEON, C. PHILLIP MILLER, Councilors. 1936 ALPHONSE R. DOCHEZ, President; C. PHILLIP MILLER, Vice-President; SHIELDS WARREN, Secretary-Treasurer; MORTON McCUTCHEON, ERNEST W. GOODPASTURE, Councilors. 1937 C. PHILLIP MILLER, President; MORTON McCUTCHEON, Vice-President; PAUL R. CANNON, Secretary-Treasurer; ERNEST W. GOODPASTURE, SHIELDS WARREN, Councilors. 1938 MORTON McCUTCHEON, President; ERNEST W. GOODPASTURE, Vice-President; PAUL R. CANNON, Secretary-Treasurer; SHIELDS WARREN, JESSE L. BOLLMAN, Councilors. 1939 ERNEST W. GOODPASTURE, President; SHIELDS WARREN, Vice-President; PAUL R. CANNON, Secretary-Treasurer; JESSE L. BOLLMAN, BALDUIN LUCKÉ, Councilors. 1940 SHIELDS WARREN, President; JESSE L. BOLLMAN, Vice-President; H. P. SMITH, Secretary-Treasurer; BALDUIN LUCKÉ, PAUL R. CANNON, Councilors. 1941 JESSE L. BOLLMAN, President; BALDUIN LUCKÉ, Vice-President; H. P. SMITH, Secretary-Treasurer; PAUL R. CANNON, DOUGLAS H. SPRUNT, Councilors. 1942, 1943, 1944 BALDUIN

LUCKÉ, President; PAUL R. CANNON, Vice-President; H. P. SMITH, Secretary-Treasurer; DOUGLAS H. SPRUNT, FRIEDA S. ROBSCHETZ-ROBBINS, Councilors.

## CONSTITUTION

### ARTICLE I.—Name

The Society shall be named "THE AMERICAN SOCIETY FOR EXPERIMENTAL PATHOLOGY."

### ARTICLE II.—Object

The object of this Society is to bring the productive investigators in pathology, working essentially by experimental methods, in closer affiliation with the workers in the other fields of experimental medicine.

### ARTICLE III.—Time and Place of Meeting

The Society shall meet at the same time and place as the Federation of American Societies for Experimental Biology, which comprises at present the American Physiological Society, the American Society of Biological Chemists, the American Society for Pharmacology and Experimental Therapeutics, and the American Society for Experimental Pathology.

### ARTICLE IV.—Membership

**SECTION 1.** Any American investigator who, through the use of experimental methods, has, within three years prior to his candidacy, contributed meritorious work in pathology, is eligible to membership.

**SEC. 2.** It shall be the policy of the Society to restrict its membership to as small numbers as is compatible with the maintenance of an active existence.

**SEC. 3.** There shall be two classes of members: active and honorary members.

**Active members:** Candidates for active membership shall be nominated at or before an annual meeting by two members of the Society. The nominators shall present to the Secretary in writing evidence of the candidate's qualifications for membership. Nominations approved by the Council shall be presented to the Society for election at the next annual meeting following nomination. For election a favorable ballot by a majority of the members present is necessary.

**Honorary members:** These may be elected from the active list or from the group of distinguished investigators at home or abroad who have contributed to the knowledge of pathology by experimental study. They shall be elected only by the unanimous vote of the members present at time of nomination.

**SEC. 4.** Active members shall pay such annual dues as are determined upon, from year to year, by

the Council. Honorary members shall pay no dues, are not eligible to office, and have no vote in the business affairs of the Society, but they shall have all the privileges of the active members in the scientific proceedings.

**SEC. 5.** Upon failure of an active member to pay dues for two years, notice shall be given to the member by the Secretary. At the end of the third year, if dues are still unpaid, such failure constitutes forfeiture of membership.

**SEC. 6.** A motion for expulsion of a member must be thoroughly investigated by the Council; at this investigation the accused shall be afforded a hearing or may be represented by a member. Expulsion can be accomplished only after a unanimous vote by the Council in favor of expulsion, sustained by a four-fifths vote of the members present at the meeting.

### ARTICLE V.—Officers

The management of the Society shall be vested in a Council of five members, consisting of a President, a Vice-President, a Secretary-Treasurer, and two other members who shall be nominated by the Council and elected by the Society. Officers are elected by a majority vote. Vacancies shall be filled by the Council for the unexpired term.

The President and Vice-President shall hold office for one year and are ineligible for re-election during the following year. The Secretary-Treasurer is eligible for re-election. Councilors shall hold office for two years and are elected on alternate years. At the first election one Councilor shall be elected for a short term of one year.

### ARTICLE VI.—Quorum

**SECTION 1.** Three constitute a quorum of the Council. The Council decides by a majority vote.

**SEC. 2.** A quorum of the Society for transaction of business shall be one-fourth of the total membership. In all questions brought before the Society a majority vote of those present shall decide, except as elsewhere provided for.

### ARTICLE VII.—Annual Meeting

**SECTION 1.** Papers shall be limited to ten minutes. However, on motion and with unanimous consent, the time may be prolonged by a period not exceeding five minutes. The Council may make provision for longer papers on suitable occasions.

**SEC. 2.** The subjects of papers must be confined to experimental work in pathology. In doubtful cases a liberal interpretation by the President and Secretary may prevail. The Council may invite, however, presentations dealing with any subject which it considers of considerable interest to the Society.

**ARTICLE VIII.—*Change of Constitution***

A motion concerning a change of the Constitution must be presented to the Council in writing by three members, and must be communicated to the members by the Secretary at least four weeks before the annual meeting. At this meeting such a change may be established when accepted by a four-fifths vote of the members present.

**BY-LAWS**

1. There must be in each year at least one meeting of the Council, which shall take place not later than the evening before the annual meeting.

2. At the end of the first session of the annual meeting the Secretary shall read the report of the Council. This report shall include (1) names of

persons recommended for membership, (2) nominations for offices, (3) matters of general interest. The Secretary shall exhibit in a conspicuous place the names of candidates for membership recommended by the Council, together with the evidence of the qualifications of the candidates.

3. The election of officers and of new members, changes in the Constitution, etc., shall be voted upon at the end of the first session.

4. Changes in the By-Laws may be determined by a majority vote of those present.

5. In the year that a new Secretary-Treasurer is elected the incoming Council Member elected that year, or another member of the Council, shall become Assistant Secretary-Treasurer for the duration of the term of the Secretary-Treasurer.

**THE AMERICAN INSTITUTE OF NUTRITION**

*Founded April 11, 1933; Incorporated November 16, 1934  
Member of Federation 1940*

**OFFICERS ELECTED 1945**

*President—Wm. C. ROSE*

*Vice-President—ARTHUR H. SMITH*

*Secretary—H. E. CARTER*

*Treasurer—E. M. NELSON*

*Councilors—T. H. JUKES, C. A. ELVEHJEM and D. W. WOOLLEY*

*Nominating Committee—A. G. HOGAN, Chairman, H. GOSS, A. D. HOLMES, I. MCQUARRIE, and LYDIA J. ROBERTS.*

**PAST OFFICERS**

1933 L. B. MENDEL, President; H. C. SHERMAN, Vice-President; J. R. MURLIN, Secretary-Treasurer; E. F. DUBoIS, M. S. ROSE, Councilors. 1934 J. R. MURLIN, President; E. F. DuBois, Vice-President; ICIE G. MACY, Secretary; W. M. BOOTHBY, Treasurer; A. H. SMITH, AGNES FAY MORGAN, R. M. BETHKE, Councilors. 1935 J. R. MURLIN, President; E. F. DuBois, Vice-President; ICIE G. MACY, Secretary; G. R. COWGILL, Treasurer; A. H. SMITH, R. M. BETHKE, L. A. MAYNARD, Councilors. 1936 E. F. DuBois, President; MARY SWARTZ ROSE, Vice-President; G. R. COWGILL, Treasurer; ICIE G. MACY, Secretary; R. M. BETHKE, L. A. MAYNARD, C. A. ELVEHJEM, Councilors. 1937 MARY S. ROSE, President; E. V. McCOLLUM, Vice-President; G. R. COWGILL, Treasurer; ICIE G. MACY, Secretary; L. A. MAYNARD, C. A. ELVEHJEM, P. E. HOWE, Councilors. 1938 E. V. McCOLLUM, President; T. M. CARPENTER, Vice-President; G. R. COWGILL, Treasurer; L. A. MAYNARD, Secretary; C. A. ELVEHJEM, P. E. HOWE, HELEN S. MITCHELL, Councilors. 1939 H. C. SHERMAN, President; T. M. CARPENTER,

Vice-President; G. R. COWGILL, Treasurer; L. A. MAYNARD, Secretary; P. E. HOWE, HELEN S. MITCHELL, A. H. SMITH, Councilors. 1940 THORNE M. CARPENTER, President; A. G. HOGAN, Vice-President; L. A. MAYNARD, Secretary; W. H. SEBRELL, JR., Treasurer; HELEN S. MITCHELL, ARTHUR H. SMITH, LYDIA J. ROBERTS, Councilors. 1941 A. G. HOGAN, President; L. A. MAYNARD, Vice-President; ARTHUR H. SMITH, Secretary; W. H. SEBRELL, JR., Treasurer; T. H. JUKES, LYDIA J. ROBERTS, H. B. LEWIS, Councilors. 1942 L. A. MAYNARD, President; H. B. LEWIS, Vice-President; ARTHUR H. SMITH, Secretary; W. H. SEBRELL, JR., Treasurer; LYDIA J. ROBERTS, GENEVIEVE STEARNS, T. H. JUKES, Councilors. 1943 H. B. LEWIS, President; ICIE G. MACY-HOOBLER, Vice-President; ARTHUR H. SMITH, Secretary; LYDIA J. ROBERTS, GENEVIEVE STEARNS, T. H. JUKES, Councilors. 1944 ICIE G. MACY-HOOBLER, President; WM. C. ROSE, Vice-President; ARTHUR H. SMITH, Secretary; E. M. NELSON, Treasurer; GENEVIEVE STEARNS, T. H. JUKES and C. A. ELVEHJEM, Councilors.

**CONSTITUTION**

1. The name of the proposed society is the "AMERICAN INSTITUTE OF NUTRITION."

2. The purposes of the society are to further the extension of the knowledge of nutrition and to facilitate personal contact between investigators in nutrition and closely related fields of interest.

3. The management of the American Institute of Nutrition shall be vested in a council consisting of the President, Vice-President, Secretary, Treasurer and three additional members.

**BY-LAWS****ARTICLE I—Membership**

**SECTION 1. Eligibility for membership:** Members. Qualified investigators who have independently conducted and published meritorious original investigations in some phase of the chemistry or physiology of nutrition and who have shown a professional interest in nutrition for at least 5 years shall be eligible for membership in the Society.

**SEC. 2. Nomination:** Nominations for membership shall be made and seconded by members of the Society on blanks furnished by the Secretary. Nominations shall be submitted to the Council who shall determine eligibility and make recommendation to the Society at a regular meeting.

**SEC. 3. Election to membership:** A. A nominee for membership may be voted for by ballot at any meeting of the Society after the Council has reported its findings on his eligibility. B. A majority of the ballots cast shall elect.

**SEC. 4. Forfeiture:** If a majority of the Council after due notice to the member in question and opportunity for a hearing, shall decide that the interests of the Society require the expulsion of a member, the Secretary shall send a notice of this decision to each member at least two weeks before the next annual meeting. At this meeting the Secretary shall, on behalf of the Council, propose the expulsion; and if two-thirds of the members present vote for it, the member shall be expelled, his assessment for the current year shall be returned to him, and he shall cease to be a member of the Society.

**ARTICLE II—Meetings and Quorum**

**SECTION 1. Annual:** The annual meeting of the Society shall be held on the date fixed by the Certificate of Incorporation.

**SEC. 2. Special:** A special meeting may be called at any time by the President, or in case of his absence or disability, by the Vice-President, and must be called at the request in writing of a majority of the Council or fifty members of the Society. Notice specifying the purpose of such meeting shall be mailed to each member at least ten days previous thereto. The Council shall select the places at which meetings shall be held.

**SEC. 3. Quorum:** Thirty members shall constitute a quorum at all meetings of the Society, but in the absence of a quorum any number shall be sufficient to adjourn to a fixed date.

**ARTICLE III—Officials**

**SECTION 1. Officers:** The officers shall be a President, and a Vice-President, who shall be elected annually, and a Secretary and Treasurer, each of whom shall be elected to serve for a term of three

years. These officers shall be elected by the members of the Society. Their terms of office shall commence on July 1 of the year in which they are elected.

**SEC. 2. Council:** The officers so selected and three additional members, one of whom shall be elected at each annual meeting to serve a term of three years, shall constitute a Board of Trustees and shall be known as 'The Council.' (When this provision is first put into effect one member shall be elected for 1 year, one for 2 years and the third for 3 years.)

**SEC. 3. Duties of Officers:** The powers and duties of the officers elected by the Society shall be such as usually devolve upon their respective positions.

**ARTICLE IV—The Council**

**SECTION 1. Powers:** The general management of the Society during the intervals between meetings shall be vested in the Council, which shall regularly perform the ordinary duties of an executive committee and possess all the powers conferred upon the Board of Trustees of an educational institution chartered by the Education Department of the University of the State of New York. A permanent charter was issued to the American Institute of Nutrition under date of November 16, 1934.

**SEC. 2. Reports:** The Council shall report to the Society its findings on the eligibility of candidates for membership, and on all charges of a violation of these By-Laws.

**ARTICLE V—Nominating Committee**

**SECTION 1. Membership:** A. The Nominating Committee shall consist of five members appointed for the coming year by the retiring President. Members who have served on the Nominating Committee for two consecutive years shall be ineligible for reappointment until after a lapse of one year. B. The President shall designate one member to be Chairman of the Nominating Committee.

**SEC. 2. Nomination of Officials:** A. The Nominating Committee shall make at least one nomination for each of the four offices, for each of the additional positions on the Council to be filled by vote of the members and for each of the positions on the Editorial Board to be vacated at the time of the annual meeting. Any member of the Institute may submit nominations to the Nominating Committee for its consideration along with those nominations made by the members of the Nominating Committee. B. The nominations by the Nominating Committee shall be transmitted to the Secretary at least six weeks before the annual meeting at which they are to be considered. C. The Secretary shall send to every member, at least two weeks before the annual meeting, a printed ballot containing the list of nominees and space for such additional

names as the member wishes to propose, and at the same time shall notify the members that they may vote by mail, returning to the Secretary the marked ballot in the envelope provided, at such a time and place as the Secretary may designate, or the ballot may be delivered to the Secretary at the beginning of the business session at which the elections are to take place.

**SEC. 3. Election of Officials:** A. At the beginning of the business session the Secretary shall present to the tellers, appointed by the President, the ballots submitted by the members and the ballots cast shall be counted forthwith. B. A majority of votes cast shall be necessary to elect an official.

**SEC. 4. Filling of Vacancies:** A. The Nominating Committee shall fill all vacancies in elective positions except such as may occur at a meeting of the Society. B. The President of the Society shall fill all vacancies in appointive positions.

#### ARTICLE VI—*Financial*

**SECTION 1. Dues:** The dues shall be the annual cost of subscription to The Journal of Nutrition for members plus an annual assessment which shall be determined by majority vote at the annual meetings, upon recommendation of the Council, and shall be due within a month after the annual meeting. A member on attaining the age of 65 may elect to be relieved from all financial obligations to the Institute including subscription to the Journal of Nutrition.

**SEC. 2. Expenditures:** No expenditures from the general funds of the Society except those required in the performance of the ordinary official duties shall be made except by vote of the Society or the Council.

**SEC. 3. Penalty for non-payment of dues:** A. Members in arrears for dues for two consecutive years shall forfeit their membership. B. Delinquent members may be reinstated by the Council provided all indebtedness to the Society is liquidated.

#### ARTICLE VII—*The Journal of Nutrition*

**SECTION 1.** The American Institute of Nutrition designates The Journal of Nutrition as its official organ of publication.

**SEC. 2.** In accordance with the expressed wish of the Wistar Institute of Anatomy and Biology,

owner and publisher of The Journal of Nutrition, the American Institute of Nutrition shall nominate members of the Editorial Board for its official organ. A. The editorial management of The Journal of Nutrition shall be vested in an Editorial Board consisting of an Editor and twelve Board Members. B. The Editor shall be chosen by the Editorial Board to serve a term of five years beginning July 1 of the year in which he is chosen, and shall be eligible for re-election. The Editor shall have the power to designate one of the Board Members to serve as his assistant, and such an appointee shall be called Associate Editor. C. Three members of the Institute shall be nominated by the Nominating Committee for membership on the Editorial Board each year to serve a term of four years, replacing three retiring members and taking office May 1 of the year in which they are elected. In the event of a vacancy in the membership of the Editorial Board occurring through death or other reason, the Nominating Committee, for each such vacancy to be filled shall make an additional nomination. In this event the nominees elected who receive the greatest number of votes shall serve the longest term of vacancies to be filled. D. Retiring members of the Editorial Board shall not be eligible for renomination until one year after their retirement.

#### ARTICLE VIII—*Papers on Scientific Subjects*

**SECTION 1.** The Secretary shall be authorized to arrange programs for the scientific sessions at the annual meetings.

#### ARTICLE IX—*Changes in Constitution and By-Laws*

**SECTION 1.** Proposed changes in the Constitution and By-Laws must be sent in writing to the Secretary at least one month before the date of the meeting at which they are to be considered, and must be signed by at least three members. The Secretary shall send a printed copy of any proposed change to each member at least two weeks before the next meeting and shall notify all members that they may vote by proxy.

**SEC. 2.** If at this meeting two-thirds of the votes cast shall favor the proposed change, it shall be made.

## THE AMERICAN ASSOCIATION OF IMMUNOLOGISTS

*Founded June 19, 1913; Member of Federation 1942*

### OFFICERS ELECTED 1942

*President*—JACQUES J. BRONFENBRENNER, Washington University School of Medicine, St. Louis, Mo.

*Secretary-Treasurer*—ARTHUR F. COCA, Pearl River, N. Y.

*Council*—JACQUES J. BRONFENBRENNER, ARTHUR F. COCA, MICHAEL HEIDELBERGER, 620 W. 168 St., New York City, PAUL R. CANNON, University of Chicago, Chicago, Ill., KARL F. MEYER, Medical Center, San Francisco, Cal., GEORGE P. BERRY, University of Rochester, Rochester, N. Y., DONALD T. FRASER, Connaught Laboratories, University of Toronto, Toronto, Canada, SANFORD B. HOOKER, (Ex officio), 80 East Concord St., Boston, Mass., JOHN F. ENDERS, (Ex officio), Harvard University School of Medicine, Boston, Mass.

### PAST OFFICERS

*Presidents*—1913 GERALD B. WEBB. 1915 JAMES W. JOBLING. 1916 RICHARD WEIL. 1917 JOHN A. KOLMER. 1918 WILLIAM H. PARK. 1919 HANS ZINSSER. 1920 RUFUS I. COLE. 1921 FREDERICK P. GAY. 1922 GEORGE W. MCCOY. 1923 H. GIDEON WELLS. 1924 FREDERICK G. NOVY. 1925 WILFRED H. MANWARING. 1926 LUDVIG HEKTOEN. 1927 KARL LANDSTEINER. 1928 EUGENE L. OPIE. 1929 OSWALD T. AVERY. 1930 STANHOPE BAYNE-JONES. 1931 ALPHONSE R. DOCHÉZ. 1932 AUGUSTUS B. WADSWORTH. 1933 THOMAS M. RIVERS. 1934 FRANCIS G. BLAKE. 1935 WARFIELD T. LONGCOPE. 1936 SANFORD B. HOOKER. 1937 CARL TENBROECK. 1938 DONALD T. FRASER. 1939 GEORGE P. BERRY. 1940 PAUL R. CANNON. 1941 KARL F. MEYER. 1942, 1943 JACQUES J. BRONFENBRENNER.

*Vice-Presidents*—1913-1915 GEORGE W. ROSS. 1915 GEORGE P. SANBORN. 1916 JOHN A. KOLMER.

*Secretary*—1913-1918 MARTIN J. SYNOTT.

*Treasurer*—1913-1918 WILLARD J. STONE.

*Secretary-Treasurer*—1918—date, ARTHUR F. COCA.

### CONSTITUTION AND BY-LAWS

*Adopted April 6, 1917*

#### ARTICLE I

**SECTION 1.** This Association shall be called "The American Association of Immunologists."

**SEC. 2.** The purpose of the Association shall be to study the problems of immunology and its application to clinical medicine.

#### ARTICLE II

**SECTION 1.** The Association shall be governed by a Council of seven, which shall consist of the

officers of the association and enough active members to make a total of seven members.

**SEC. 2.** The officers of the Association shall be a President, a Secretary, and a Treasurer, who shall be nominated annually by the Council, and elected by the Society to serve for one year. Nominations of officers may be made also by members of the Society.

**SEC. 3.** No councilor is eligible for re-election until after one year, except the Secretary and the Treasurer, who are eligible for re-election.

**SEC. 4.** If any councilor without good and sufficient reason fails to attend two consecutive meetings of the Council he shall be considered to have resigned.

**SEC. 5.** The same person shall not serve as President more than one year consecutively.

**SEC. 6.** It is the duty of the Council to conduct the business of the Association and to elect the new members. Should a vacancy occur in the Council otherwise than by the expiration of the term of service, the Council may elect a member to serve for the unexpired portion of the term.

### ARTICLE III

**SECTION 1. Active Members.** Any one actively engaged in the systematic study of problems relating to immunology shall be eligible to active membership.

### ARTICLE IV

Candidates for membership shall be nominated by two active members of the Association who shall present in writing to the Council evidence of the fitness of the candidates to become members of the Association.

### ARTICLE V

If a majority of the Council shall decide that the interests of the Society require the expulsion of a member, the Secretary shall send a notice of this decision to each active member at least two weeks before the next annual meeting. At this meeting the Secretary shall, on behalf of the Council, propose the expulsion; and if two-thirds of the members present vote for it, the member shall be expelled, his assessment for the current year shall be returned to him, and he shall cease to be a member of the Society.

### ARTICLE VI

**SECTION 1.** A quorum of the Council for the transaction of all business shall be three.

**SEC. 2.** Any number of members present at the time appointed for the annual meeting of the Association, shall constitute a quorum.

**BY-LAWS**

1. A regular meeting of the Association shall be held annually at such time and place as the Council shall determine.

2. Special meetings of the Association may be held at the discretion of the Council.

3. These regular and special meetings shall be open to all members of the Association.

4. A meeting of the Council shall be held shortly before each annual session of the Association.

5. Hereafter each Councilor shall serve for a period of six years. Under this rule the service of one member and also that of the Secretary-Treasurer terminates at the meeting of 1936. At that meeting two members shall be elected to the Council, one of whom may serve as Secretary-Treasurer. Thereafter the period of service of these two members shall run concurrently; hence, two members must be elected to the Council every six years in order to maintain a membership of seven.

6. Past Presidents are honorary members of the Council.

7. The titles of all communications to be pre-

sented before the Association shall be approved by the Council.

8. Failure of an active member to offer a paper at least once in three years shall be equivalent to resignation. If in its judgment there is sufficient reason the Council may, in individual cases, suspend this rule.

9. The dues of the Association shall be fixed annually by the Council.

10. Failure to pay dues for three successive years shall constitute annulment of membership.

11. The constitution and by-laws may be amended by a two-thirds vote of the active members present at any regular meeting.

12. No amendment shall be adopted at the meeting at which it is proposed.

13. The Journal of Immunology, which is the property and official organ of this Association, shall be administered for the Association by an editorial staff to consist of an Editor-in-Chief and at least three Associate Editors, with the advice of a Board of Editors.

14. The members of the editorial staff shall be elected or may be removed by a majority vote of the Council of the Association.

## ALPHABETICAL LIST OF ALL MEMBERS OF THE SIX SOCIETIES

The parenthesis following each listed name gives the Society affiliation and year of election:

- (1) The American Physiological Society\*
  - (2) The American Society of Biological Chemists
  - (3) The American Society for Pharmacology and Experimental Therapeutics
  - (4) The American Society for Experimental Pathology
  - (5) The American Institute of Nutrition
  - (6) The American Association of Immunologists
- 

## HONORARY MEMBERS

- Castaneda, M. Ruiz, M.D. Investigaciones Medicas, Hospital General, Mexico, D. F. Director, Department of Medical Research. (6, 1942)
- Chopra, R. N., M.A., M.D., Sc.D.(Cantab), F.R.C.P. (London) P.I.E. School of Tropical Medicine, Calcutta, India. Director; Professor of Pharmacology. (3, 1938)
- Dale, H. H. Medical Research Council, National Institute for Medical Research, Hampstead, London, N.W. 3, England. Director, National Institute for Medical Research. (3, 1926)
- Flexner, Simon, M.D., Sc.D.(hon.), LL.D. 520 E. 86th St., New York City. Emeritus Director, Rockefeller Institute for Medical Research. (6, 1920)
- Hektoen, Ludvig, M.D. 629 S. Wood St., Chicago, Ill. President, Chicago Tumor Institute. (6, 1919)
- Hitchens, Arthur P., M.D. Medical School, University of Pennsylvania, Philadelphia. Professor of Public Health and Preventive Medicine; Lt. Col., M.C., U.S.A. (6, 1913)
- Houssay, Bernardo A., M.D. Viamonte 2790, Buenos Aires, Argentina. (1, 1942)
- Hunton, F. M., M.D. Woodbridge, Conn. (6, 1918)
- Loewi, Otto, M.D. New York University College of Medicine, 477 First Ave., New York City. Research Professor in Pharmacology. (3, 1941)
- McCoy, George Walter, M.D. Louisiana State University Medical School, New Orleans. Director, Department of Public Health. (6, 1916)
- Novy, Frederick G., M.D., Sc.D., LL.D. 721 Forest Ave., Ann Arbor, Mich. Dean Emeritus and Professor Emeritus of Bacteriology, Medical School, University of Michigan. (6, 1920)
- Rosenau, Milton J., M.D., A.M. Medical School, University of North Carolina, Chapel Hill. Director, School of Public Health; Professor of Epidemiology, School of Public Health. (6, 1918)

Sherrington, Sir Charles S., O.M., Sc.D., M.D., F.R.S. "Broomside," Valley Road, Ipswich, England. Former Waynflete Professor of Physiology, Oxford University; Former President of the Royal Society. (1, 1904)

Sordelli, A. Institute of Bacteriology, Department of Public Health, Buenos Aires, Argentina. Director. (6, 1942)

Straub, Walther, M.D. University of Munich, Germany. (3, 1927)

## MEMBERS

- Abels, Jules C., M.D. Memorial Hospital, 444 E. 68th St., New York City. Assistant Attending Physician. (4, 1944)
- Abramson, David I., M.D. Mayo General Hospital, Galesburg, Ill. Capt. M.C. (1, 1937)
- Abramson, Harold A., M.D. 133 E. 58th St., New York City. Assistant Professor of Physiology, College of Physicians and Surgeons, Columbia University. (1, 1930; 2, 1934)
- Abreu, Benedict E., M.S., Ph.D., Division of Pharmacology, Univ. of California Medical School, San Francisco. Assistant Professor of Pharmacology. (3, 1941)
- Acheson, George H., M.D. Harvard Medical School, 25 Shattuck St., Boston, Mass. Associate in Pharmacology. (1, 1942; 3, 1945)
- Adams, Mildred, M.A., Ph.D. Takamine Laboratory, Clifton, N. J. Research Chemist. (2, 1934)
- Adams, R. Charles, M.D., C.M., M.S. (Anesthesiology), Mayo Clinic, Rochester, Minn. Instructor in Anesthesia, Mayo Foundation, University of Minnesota. Member of Mayo Clinic Staff, Section on Anesthesia. (3, 1942)
- Adams, W. Lloyd, M.A., Ph.D. Albany Medical College, 357 Morris St., Albany, N. Y. Assistant Professor of Physiology and Pharmacology. (3, 1942)
- Addis, Thomas, M.D., M.R.C.P. Lane Hospital, San Francisco, Calif. Professor of Medicine, Stanford University. (1, 1922)
- Addison, William H. F., M.D. School of Medicine, University of Pennsylvania, Philadelphia. Professor of Histology and Embryology. (1, 1928)

\* Recommended by the Council of the American Physiological Society for election at the next annual meeting of the Society.

- Ades, Harlow Whiting, Ph.D.\* Box 731, Emory University, Ga. (1, 1945)
- Adler, Harry F., M.S., Ph.D., M.D. Dept. Physiology, S. A. M., Randolph Field, Texas. (1, 1943)
- Adolph, Edward Frederick, Ph.D. School of Medicine and Dentistry, University of Rochester, Rochester, N. Y. Associate Professor of Physiology. (1, 1921)
- Adolph, William H., Ph.D. School of Nutrition, Cornell University, Ithaca, N. Y. (5, 1934)
- Ahlquist, Raymond P., M.S., Ph.D. Dept. of Pharmacology, Univ. of Georgia School of Medicine, Augusta. Assistant Professor of Pharmacology. (3, 1945)
- Albanese, Anthony A., Ph.D. G-7 Tower Lab., Children's Medical Service, Bellevue Hospital, New York, N. Y. Assistant Professor of Pediatric Biochemistry, New York University College of Medicine. (2, 1944)
- Albritton, Errett C., M.D. George Washington University Medical School, 1339 H St., N.W., Washington, D. C. Professor of Physiology and Head of the Department of Physiology. (1, 1933)
- Algire, Glenn H., M.D. National Cancer Institute, Bethesda, Md. Senior Assistant Surgeon, U.S. Public Health Service. (4, 1945)
- Allan, Frank N., M.D. Lahey Clinic, 605 Commonwealth Ave., Boston, Mass. Co-director of the Medical Department. (4, 1930)
- Allen, Charles Robert, Ph.D.\* University of Texas, School of Medicine, Galveston. Assistant Professor of Department of Anesthesiology. (1, 1943)
- Allen, Frederick M., M.D. 1031 Fifth Ave., New York City. Professor of Medicine, Polyclinic Medical School and Hospital. (1, 1924; 4, prior to 1920)
- Allen, J. Garrett, M.D.\* University of Chicago, University Clinics, Chicago, Ill. Instructor in Surgery. (1, 1943)
- Allen, Lane, M.S., Ph.D., M.D. University of Georgia School of Medicine, University Place, Augusta. Associate Professor of Anatomy. (1, 1939)
- Allen, Shannon C., Ph.D.\* 1933 Victoria Ave., Dayton, O. Captain, A.C. (1, 1945)
- Allen, Willard M., M.D. Washington University School of Medicine, 630 S. Kingshighway Blvd., St. Louis, Mo. Professor of Obstetrics and Gynecology. (1, 1934)
- Allen, William F., Ph.D., D.Sc. University of Oregon Medical School, Portland. Professor of Anatomy. (1, 1929)
- Alles, Gordon A., M.S., Ph.D. 770 S. Arroyo Parkway, Pasadena, Calif. Lecturer in Pharmacology, University of California Medical School, San Francisco, and Research Associate in Biology, California Institute of Technology, Pasadena. (1, 1932; 3, 1941)
- Almquist, Herman J., Ph.D. F. E. Booth Co. Laboratories, 1290 Powell St., Emeryville, Calif. Director of Research. (2, 1937; 5, 1937)
- Alvarez, Walter C., M.D. Mayo Clinic, Rochester, Minn. Professor of Medicine, Mayo Foundation. (1, 1917; 3, 1921)
- Alving, Alf Sven, M.D. Billings Hospital, University of Chicago, 950 E. 59th St., Chicago, Ill. Associate Professor of Medicine. (1, 1939)
- Amberg, Samuel, M.D., F.A.A.P. Mayo Clinic, Rochester, Minn. Associate in Pediatrics, Mayo Clinic; Associate Professor of Pediatrics, Mayo Foundation (1, 1903; 2, 1906; 3, 1909)
- Amberson, William R., Ph.D. University of Maryland School of Medicine, Baltimore. Professor of Physiology. (1, 1924)
- Ambrose, Anthony M., M.S., Ph.D. Western Regional Research Laboratory, 800 Buchanan St., Albany, Calif. Pharmacologist, U. S. Department of Agriculture, Bureau of Agricultural Chemistry and Engineering. (3, 1937)
- Amoss, Harold L., M.D., M.S., Dr.P.H., Sc.D. 21 Field Point Road, Greenwich, Conn. (4, 1922; 6, 1917)
- Anderesch, Marie A., Ph.D. University Hospital, Baltimore, Md. Biochemist, University Hospital, Instructor in Medicine, University of Maryland. (2, 1940)
- Andersen, Dorothy H., M.D. Babies Hospital, Broadway and 167th St., New York City. Associate in Pathology, Columbia University. (4, 1935)
- Anderson, Evelyn M., M.A., M.D. University of California Hospital, San Francisco. Assistant Professor of Medicine. (1, 1934)
- Anderson, Hamilton H., M.S., M.D. Pharmacology Laboratory, Univ. of California Medical School, San Francisco. Professor of Pharmacology. (3, 1931)
- Anderson, Oscar Daniel, Ph.D. Stimson Hall, Cornell University, Ithaca, N. Y. Assistant Professor of Physiology. (1, 1939)
- Anderson, Rudolph J., Ph.D. Sterling Laboratory, Yale University, New Haven, Conn. Professor of Chemistry. (2, 1915)
- Anderson, W. A. D., M.A., M.D. Marquette University School of Medicine, Milwaukee, Wis. Professor of Pathology and Bacteriology. (4, 1941)
- Anderson, William E., M.A. Eastern State Farmers' Exchange, Westbrook Farm, Rockville, Conn. Biochemist. (2, 1931; 5, 1933)
- Andermont, H. B., Sc.D. National Cancer Institute, Bethesda, Md. Principal Biologist, U. S. Public Health Service. (4, 1939)
- Andrews, James C., Ph.D. University of North Carolina, Chapel Hill. Professor of Biological Chemistry and Nutrition. (2, 1925)
- Andrus, E. Cowles, M.D. Johns Hopkins Hospital, Baltimore, Md. Assistant Visiting Physi-

- cian; Associate Professor of Medicine, Johns Hopkins University. (1, 1925)
- Angerer, Clifford**, Ph.D.\* Ohio State University, Columbus. Instructor in Physiology. (1, 1943)
- Angevine, D. Murray**, M.D. Alfred I. du Pont Institute, Wilmington, Del. Pathologist; Visiting Assistant Professor of Pathology, University of Pennsylvania. (4, 1940)
- Angier, Roswell Parker**, Ph.D. c/o Los Ranchos Perkins, Tucson, Ariz. Professor of Psychology, Yale University. (1, 1906)
- Ansbacker, Stefan**, M.S., D.Sc. American Home Products Corp., Products Development Lab., 350 Fifth Ave., New York City. Scientific Director. (2, 1939)
- Anson, Mortimer L.**, Ph.D. Continental Foods, Inc., Hoboken, N. J. Director of Chemical Research. (2, 1937)
- Apperly, Frank L.**, M.A., D.Sc., M.D.; F.R.C.P. Medical College of Virginia, Richmond. Professor of Pathology. (4, 1936)
- Arkin, Aaron**, M.A., M.D., Ph.D. Suite 2006, 25 E. Washington St., Chicago, Ill. Rush Professor of Medicine, U. of Ill. Prof. and Chairman, Dept. of Medicine, Cook County Graduate School. (1, 1914; 3, 1919)
- Armstrong, Philip B.**, M.D.\* College of Medicine, Syracuse Univ., Syracuse 10, N. Y. Professor of Anatomy. (1, 1945)
- Armstrong, W. D.**, M.S., M.D., Ph.D. Medical Sciences Bldg., University of Minnesota, Minneapolis. Professor of Physiological Chemistry. (2, 1938)
- Arnold, Lloyd**, A.M., M.D. 1538 E. 57th St., Chicago, Ill. (4, 1930; 6, 1925)
- Arnow, L. Earle**, Ph.D., M.D. Medical Research Division, Sharp and Dohme, Glenolden, Pa. Director of Research. (2, 1940)
- Aronson, Joseph D.**, M.D. Phipps Institute, University of Pennsylvania, Philadelphia 4. Associate Professor of Bacteriology. (4, 1927; 6, 1925)
- Artom, Camillo**, M.D. Bowman Gray School of Medicine, Winston-Salem, N. C. Professor of Biochemistry. (2, 1944)
- Ascham, Leah**, Ph.D. Kansas State College, Manhattan. Professor, School of Home Economics. (5, 1935)
- Asenjo, Conrado F.**, Ch.E., M.S., Ph.D. Dept. of Chemistry, School of Tropical Medicine, San Juan, Puerto Rico. Associate Professor of Chemistry, School of Tropical Medicine of the University of Puerto Rico under the Auspices of Columbia University. (2, 1941)
- Ashby, Winifred M.**, Ph.D. 305 10th St., N.E., Washington, D. C. Senior Scientist, Federal Security Agency (St. Elizabeth's Hospital). (6, 1923)
- Ashman, Richard**, M.S., Ph.D. School of Medicine, Louisiana State University, New Orleans. Professor of Physiology. (1, 1925)
- Astwood, Edwin Bennet**, M.D., C.M., Ph.D. Pratt Diagnostic Hospital, 30 Bennet St., Boston, Mass. Research Professor of Medicine at Tufts Medical School. (1, 1939)
- Aub, Joseph C.**, M.D. Massachusetts General Hospital, Boston 14. (1, 1919; 5, 1933)
- Auer, John**, M.D. 1402 S. Grand Blvd., St. Louis, Mo. Professor of Pharmacology and Director of the Department, St. Louis University School of Medicine. (1, 1905; 3, 1908)
- Austin, J. Harold**, M.D. 711 Maloney Clinic, 36th and Spruce Sts., Philadelphia, Pa. Director, Pepper Laboratory. (2, 1922)
- Austin, Richard Sisson**, M.D. Cincinnati General Hospital, University of Cincinnati, Cincinnati, O. Professor of Pathology. (4, 1927)
- Avery, O. T.**, M.D., Sc.D., LL.D. Hospital of the Rockefeller Institute, 66th St. and York Ave., New York City. Member Emeritus, Rockefeller Institute for Medical Research. (4, 1921; 6, 1920)
- Axtmayer, Joseph H.**, A.M., Ph.D. School of Tropical Medicine, San Juan, Porto Rico. Associate Professor of Chemistry. (5, 1935)
- Ayo, Corrado**, M.D. 1st Lt. M.C., 309 General Hospital, Ft. Jackson, S. C. Atg. Chief Lab. Soc. (6, 1944)
- Babkin, B. P.**, M.D., D.Sc., F.R.S.C. McGill University, Montreal, Canada. Professor of Physiology. (1, 1924)
- Bachem, Albert**, Ph.D. College of Medicine, University of Illinois, 1853 W. Polk St., Chicago. Professor of Biophysics. (1, 1933)
- Bachman, Carl**, M.D. Mobile Hospital No. 5, c/o Fleet P. O., San Francisco, Calif. Lieut. Commander. (2, 1941)
- Bachmann, George**, M.S., M.D., F.A.C.P. 1088 Lullwater Road, N.E., Atlanta, Ga. Professor of Physiology, Emory University School of Medicine. (1, 1912)
- Baer, Erich**, Ph.D. Banting Institute, 100 College St., Toronto, Canada. Assistant Research Professor of Organic Chemistry, University of Toronto. (2, 1942)
- Baernstein, Harry D.**, M.S., Ph.D. National Institute of Health, Bethesda, Md. Biochemist. (2, 1934)
- Baetjer, Anna M.**, D.Sc. Johns Hopkins School of Hygiene and Public Health, 615 N. Wolfe St., Baltimore 5, Md. Assistant Professor of Physiological Hygiene. (1, 1920)
- Bahrs, Alice M.**, M.A., Ph.D. The Martha Washington Hotel, 10th and Montgomery Sts., Portland, Ore. (1, 1933)

- Bailey, Cameron Vernon, M.D., C.M. 303 E. 20th St., New York City. *Clinical Professor of Medicine, New York Post-Graduate Medical School, Columbia University.* (2, 1920; 5, 1933)
- Bailey, Orville T., M.D. Harvard University Medical School, 25 Shattuck St., Boston, Mass. *Associate in Pathology.* (4, 1939)
- Bailey, Percival, M.D., Ph.D. University of Illinois College of Medicine, 912 S. Wood St., Chicago. *Professor of Neurology and Neurosurgery.* (1, 1941)
- Baitzell, George Alfred, A.M., Ph.D. Yale University, Osborn Zoological Lab., 165 Prospect St., New Haven, Conn. *Professor of Biology.* (1, 1915)
- Baker, A. B., M.D. University of Minnesota Medical School, 126 Millard Hall, Minneapolis. *Associate Professor of Neuropsychiatry and Neuropathology.* (4, 1940)
- Baker, Roger D., M.D. Medical College of Alabama, Birmingham 5. *Professor of Pathology.* (4, 1939)
- Baldes, Edward J., A.M., Ph.D. Mayo Foundation, Rochester, Minn. *Assistant Professor of Physics, Mayo Foundation, Graduate School, University of Minnesota.* (1, 1930)
- Baldwin, Francis Marsh, A.M., Ph.D. University of Southern California, Los Angeles. *Professor of Zoology and Director of Experimental Marine Biology.* (1, 1919)
- Bale, William F., Ph.D.\* University of Rochester, School of Medicine and Dentistry, Rochester, N. Y. *Associate in Radiology.* (1, 1943)
- Ball, Eric G., M.A., Ph.D. Harvard Medical School, Boston, Mass. *Associate Professor of Biological Chemistry.* (2, 1934)
- Ball, Howard A., M.D. San Diego County General Hospital, N. Front St., San Diego, Calif. *Pathologist, San Diego County General and Paradise Valley Hospitals.* (4, 1937)
- Balls, Arnold Kent, Ph.D. Enzyme Research Laboratory, U. S. Bureau of Agricultural and Industrial Chemistry, Western Regional Research Laboratory, 800 Buchanan St., Albany 6, Calif. *Head Chemist; Adjunct Professor, The George Washington University (on leave).* (2, 1932)
- Banus, Mario Garcia, M.Sc., D.Sc. Tufts College Medical School, Boston, Mass. *Associate Professor of Physiology.* (1, 1927)
- Bard, Philip, A.M., Ph.D. Johns Hopkins University School of Medicine, 710 N. Washington St., Baltimore, Md. *Professor of Physiology; Member National Academy of Sciences.* (1, 1929)
- Barker, S. B., Ph.D. College of Medicine, State University of Iowa, Iowa City. *Assistant Professor of Physiology.* (1, 1938)
- Barlow, Orpheus W., M.D., Ph.D. R.F.D. 3 Warwick Road, Winchester, N. H. (1, 1936; 3, 1944)
- Barnes, B. O., A.M., Ph.D. 2220 S. St. Paul, Denver, Colo. *Professor of Health Education, University of Denver. Station Hospital, KAAF, Kingman, Ariz.* (1, 1932)
- Barnes, LaVerne A., M.S., Ph.D. Alta Vista Rd., Bethesda, Md. *Lieutenant, II-V(S), U.S.N.R. (Epidemiology and Sanitation Unit, National Naval Medical School).* (6, 1931)
- Barnes, Richard Henry, Ph.D. Sharp & Dohme, Glenolden, Pa. *Director of Biochemical Research, Medical Research Division.* (2, 1941; 5, 1944)
- Barnes, Thomas C., D.Sc. Hahnemann Medical College, Philadelphia, Penna. *Associate Professor of Physiology.* (1, 1942)
- Barott, Herbert G., E.E. U. S. Department of Agriculture, National Agricultural Research Center, Beltsville, Md. *Biophysicist, Animal Nutrition Division, Bureau of Animal Industry.* (5, 1938)
- Barrera, S. Eugene, M.D. Albany Medical College, New Scotland Ave., Albany, N. Y. (1, 1937)
- Barron, Donald H., M.S., Ph.D., M.A. (Cambridge)\* Yale University School of Medicine, New Haven, Conn. *Associate Professor of Physiology.* (1, 1943)
- Barron, E. S. Guzman, M.D. Department of Medicine, University of Chicago, Chicago, Ill. *Assistant Professor of Biochemistry.* (2, 1931)
- Bartley, S. Howard, Ph.D. Dartmouth Eye Institute, Dartmouth College, Hanover, N. H. *Assistant Professor of Research in Physiological Optics.* (1, 1935)
- Bass, Allan D., M.S., M.D. c/o G. C. Thompson, Manchester, Ga. *Professor of Pharmacology, Syracuse University. On leave of absence in the Service.* (3, 1944)
- Batchelder, Esther L., A.M., Ph.D. Rhode Island State College, School of Agriculture and Home Economics, Kingston. *Head of Department of Home Economics.* (5, 1933)
- Bateman, John B., Ph.D.\* Mayo Aero Medical Unit, Mayo Clinic, Rochester, Minn. *Associate.* (1, 1945)
- Bates, Robert W., Ph.D. E. R. Squibb and Sons, Biological Laboratories, New Brunswick, N. J. *Head, Endocrine Products Dept.* (2, 1936)
- Batterman, Robert C., M.D. New York University College of Medicine, 477 First Ave., New York City. *Instructor in Therapeutics.* (3, 1941)
- Baudisch, Oskar, Ph.D. Saratoga Springs, N. Y. *Director of Research, Saratoga Springs Authority, State of New York.* (2, 1931)
- Bauer, Johannes H., M.D. Rockefeller Foundation, 49 W. 49th St., New York City. *Associate Director, International Health Division of the Rockefeller Foundation.* (4, 1935)

- Bauer, Walter, M.D. Massachusetts General Hospital, Boston. Associate Professor and Tutor in Medicine, Harvard Medical School; Colonel, MC, Army Service Forces Hq. 8th Service Command, Dallas, Texas. (1, 1929)
- Bauman, Louis, M.D. Presbyterian Hospital, New York City. Assistant Professor of Clinical Medicine, Columbia University. (2, 1912)
- Baumann, Carl A., M.S., Ph.D. Biochemistry Dept., University of Wisconsin, Madison. Associate Professor of Biochemistry. (2, 1938; 5, 1938)
- Baumann, Emil J., Ph.D. 7 Church Lane, Scarsdale, N. Y. Chemist, Montefiore Hospital. (2, 1922)
- Baumberger, J. Perey, M.S., Se.D. Stanford University, Calif. Professor of Physiology. (1, 1921)
- Bayne-Jones, Stanhope, M.D. Yale University, School of Medicine, New Haven, Conn. Professor of Bacteriology. (4, 1927; 6, 1917)
- Bazett, Henry C., M.A., M.D., F.R.C.S. University of Pennsylvania, School of Medicine, Philadelphia. Professor of Physiology. (1, 1921)
- Beach, Eliot F., Ph.D. 2nd Port Headquarters, Surgeon's Office, APO 322, San Francisco, Calif. Captain, Sanitary Corps. (2, 1941; 5, 1942)
- Bean, John W., M.S., Ph.D., M.D. University of Michigan, Ann Arbor. Professor of Physiology. (1, 1932)
- Beard, Howard H., M.A., Ph.D. Chicago Medical School, 710 S. Wolcott Ave., Chicago, Ill. Professor of Biological Chemistry. (2, 1928; 5, 1933)
- Beard, Joseph W., M.D. Duke Hospital, Durham, N. C. Associate Professor of Surgery. (4, 1938; 6, 1940)
- Beazell, James Myler, Ph.D., M.D. 2118 Hayden, Amarillo, Texas. Captain, MC, AUS; Instructor in Physiology and Pharmacology, Northwestern University School of Medicine. (1, 1939)
- Beck, Claude S., M.D. Lakeside Hospital, Cleveland, O. Professor of Neurosurgery, Western Reserve University; Associate Surgeon, Lakeside Hospital. (4, 1930)
- Beck, Lyle V., M.S., Ph.D. Hahnemann Medical College, 235 N. 15th St., Philadelphia, Pa. Associate Professor of Physiology. (1, 1941)
- Becker, Ernestine, M.A. Johns Hopkins University, Baltimore, Md. Associate in Biochemistry. (5, 1938)
- Becker, R. Frederick, M.S., Ph.D. Northwestern University Medical School, 303 E. Chicago Ave., Chicago, Ill. Instructor in Anatomy. (1, 1941)
- Becker, Theodore J., M.A., Ph.D. Winthrop Chemical Co., Rensselaer, N. Y. Research Pharmacologist. (3, 1944)
- Beekman, Harry, M.D. Marquette University School of Medicine, Milwaukee, Wis. Professor and Director of the Department of Pharmacology. (3, 1937)
- Beecher, Henry K., M.D. Massachusetts General Hospital, Boston. Dorr Professor of Research in Anesthesia, Harvard Medical School; Anesthetist-in-Chief, Massachusetts General Hospital. (3, 1940)
- Behre, Jeanette Allen, Ph.D. Department of Biochemistry, College of Physicians and Surgeons, 630 W. 168th St., New York City. Associate. (2, 1925)
- Belding, David L., M.D. Boston University School of Medicine, Boston, Mass. Professor of Bacteriology and Experimental Pathology. (4, 1927)
- Belding, Harwood S., Ph.D.\* Fatigue Laboratory, Harvard University, Soldier's Field, Boston, Mass. Assistant Professor of Industrial Physiology. (1, 1945)
- Bell, E. T., M.D. 110 Anatomy Bldg., University of Minnesota, Minneapolis. Professor of Pathology. (4, 1931)
- Benedict, Francis Gano, Ph.D., Se.D., M.D. Machiasport, Me. Member of the National Academy of Sciences. (1, 1904; 2, 1906)
- Benham, Olive Ray, B.S. Connecticut State Department of Health, Bureau of Laboratories, Hartford. Chief Serologist. (6, 1944)
- Bennett, A. Lawrence, Ph.D., M.D. College of Medicine, University of Nebraska, Omaha. Professor of Physiology and Pharmacology. (1, 1941)
- Bennett, Granville A., M.D. University of Illinois College of Medicine, 1853 West Polk Street, Chicago. Professor of Pathology. (4, 1931)
- Bennett, Leslie L., M.D.\* University of California, Berkeley 4. Assistant Professor of Physiology. (1, 1945)
- Bennett, Mary Adelia, M.A., Ph.D. Lankenau Hospital Research Institute, Philadelphia, Pa. Research Biochemist. (2, 1941)
- Benson, Clara C., Ph.D. 160 Dorset St., West Port Hope, Ontario, Canada. Professor Emeritus of Food Chemistry, University of Toronto. (2, 1906)
- Berg, Benjamin N., M.D. 630 W. 168th St., New York City. Associate in Pathology, Columbia University, College of Physicians and Surgeons. (4, 1928)
- Berg, Clarence P., M.A., Ph.D. Chemistry Department, State University of Iowa, Iowa City. Professor of Biochemistry. (2, 1933; 5, 1936)
- Berg, William N., Ph.D. 225 W. 106th St., New York City. Biochemist. (2, 1906)
- Bergeim, Olaf, M.S., Ph.D. 1853 W. Polk St., Chicago, Ill. Associate Professor of Physiological Chemistry, University of Illinois College of Medicine. (1, 1916; 2, 1914)

- Bergmann, Werner, Ph.D. Sterling Chemistry Building, Yale University, New Haven, Conn. Associate Professor. (2, 1934)
- Berkson, Joseph, M.A., M.D., D.Sc. 2141 Eye St., N.W., Washington, D. C. Associate Professor, Biometry and Medical Statistics, Mayo Foundation, University of Minnesota. Col. A U.S. (1, 1933)
- Bernheim, Frederick, Ph.D. Box 3109, Duke Medical School, Durham, N. C. Associate Professor of Physiology and Pharmacology. (2, 1933; 3, 1935)
- Bernthal, Theodore G., M.S., M.D. Vanderbilt University School of Medicine, Nashville, Tenn. Associate Professor of Physiology. (1, 1932)
- Berry, George Packer, M.D. University of Rochester, Rochester, N. Y. Assistant Dean; Professor of Bacteriology; Associate Professor of Medicine. (4, 1938; 6, 1934)
- Besscy, Otto A., Ph.D. Public Health Research Institute of the City of New York, Inc., Foot of E. 15th St., New York City. Director of the Institute, Chief of the Division of Nutrition and Physiology. (2, 1938)
- Best, Charles Herbert, C.B.E., M.A., M.D., D.Sc. (London), D.Sc. (Chicago), F.R.S. University of Toronto, Toronto, Ont., Canada. Director, Banting and Best Department of Medical Research and Department of Physiology. (1, 1923; 2, 1923)
- Bethell, Frank H., M.D. 409 Lenawee Drive, Ann Arbor, Mich. Assistant Professor of Internal Medicine and Assistant Director of the Thomas Henry Simpson Memorial Institute. (4, 1936)
- Bethke, Roland M., M.S., Ph.D. Ohio Agricultural Experiment Station, Wooster. In Charge of Nutritional Investigations. (2, 1928; 5, 1933)
- Beutner, R., M.D., Ph.D. 235 N. 15th St., Philadelphia, Pa. Professor and Head of Department of Pharmacology, Hahnemann Medical College. (1, 1924; 3, 1924)
- Beyer, Karl H., Ph.D., M.D. Medical-Research Division, Sharp and Dohme, Inc., P.O. Box 7259, Glenolden, Pa. Director of Pharmacological Research. (1, 1942; 3, 1944)
- Bieter, Raymond N., M.D., Ph.D. University of Minnesota, Minneapolis. Professor of Pharmacology. (3, 1930)
- Bills, Charles E., M.A., Ph.D. Mead Johnson & Co., Evansville, Ind. Director of Research. (2, 1928; 5, 1935)
- Bing, Franklin C., Ph.D. 1135 Fullerton Ave., Chicago, Ill. Director, American Institute of Baking; Assistant Professor of Physiology, Northwestern University Medical School. (2, 1931; 5, 1934)
- Bing, Richard J., M.D. Johns Hopkins Hospital, Baltimore 5, Md. Assistant Professor of Surgery. (1, 1942)
- Binger, Carl A., M.D. 125 E. 73rd St., New York City. Assistant Professor of Clinical Medicine (Psychiatry), Cornell University Medical College. (1, 1927)
- Binkley, Stephen Bennett, M.S., Ph.D. Research Department, Parke, Davis & Co., Detroit, Mich. (2, 1941)
- Bisbey, Bertha, A.M., Ph.D. Gwynn Hall, University of Missouri, Columbia. Professor of Home Economics. (5, 1933)
- Bischoff, Fritz E., M.S., Ph.D. Cottage Hospital, Santa Barbara, Calif. Director of Research. (2, 1928; 5, 1933)
- Bishop, George H., Ph.D. Washington University Medical School, Euclid and Kingshighway, St. Louis, Mo. Professor of Bio-Physics. (1, 1923)
- Biskind, Gerson R., M.D. Mt. Zion Hospital, San Francisco, Calif. Pathologist, Mt. Zion Hospital; Clinical Instructor in Pathology, University of California Medical School. (4, 1944)
- Black, Edgar C., Ph.D.\* Dept. of Physiology, Dalhousie Univ., Halifax, Nova Scotia, Canada. (1, 1943)
- Blair, Edgar A., M.S., Ph.D. U. S. Army, General Section T.I.S., Fort Benning, Ga. Lt. Col. (1, 1936)
- Blair, Henry A., M.Sc., Ph.D. University of Rochester School of Medicine and Dentistry, Rochester, N. Y. Associate Professor of Physiology. (1, 1934)
- Blake, Francis G., M.D., M.A. (hon.), Sc.D. Yale University School of Medicine, New Haven, Conn. Dean and Sterling Professor of Medicine. (4, prior to 1920; 6, 1921)
- Blankenhorn, M. A., M.D. University of Cincinnati, Cincinnati, O. Professor of Medicine. (4, 1932)
- Blatherwick, Norman R., M.S., Ph.D., Sc.D. Metropolitan Life Ins. Co., 1 Madison Ave., New York City. Director of Biochemical Laboratory. (1, 1915; 2, 1915; 5, 1934)
- Blau, Nathan F., Ph.D. Fine Chemicals Division of Ivano, Inc., 184 Commercial St., Malden, 48, Mass. Research Chemist. (2, 1928)
- Blish, Morris J., M.A., Ph.D. Amino Products Company, Rossford, O. Research Director. (2, 1944)
- Bliss, Chester Ittner, Ph.D. Conn. Agr. Expt. Sta., P. O. Box 1106, New Haven. Biometrician, Lecturer in Biometry, Yale University. (3, 1944)
- Bliss, Eleanor A., Sc.D. Department of Preventive Medicine, Johns Hopkins Hospital, 615 N. Wolfe St., Baltimore, Md. Associate in

- Preventive Medicine, Johns Hopkins University, School of Medicine.* (6, 1931)
- Bliss, Sidney, Ph.D. Tulane University, New Orleans, La. *Professor of Biochemistry, School of Medicine.* (2, 1928)
- Bloch, Konrad, Ph.D. 630 W. 168th St., New York, N. Y. *Associate in Biochemistry, Columbia University.* (2, 1944)
- Block, Richard J., Ph.D. 15 Cooper Rd., Scarsdale, N. Y. *Director of Research, C. M. Armstrong Co.; Associate, Department of Physiology and Biochemistry, New York Medical College, Flower and Fifth Avenue Hospital.* (2, 1934; 5, 1933)
- Block, Walter D., M.S., Ph.D. University Hospital, Ann Arbor, Mich. *Assistant Professor of Biological Chemistry, Rackham Arthritis Research Unit.* (2, 1942)
- Bloom, William, M.D. 1419 E. 56th St., Chicago, Ill. *Professor of Anatomy, University of Chicago.* (4, 1930)
- Bloomfield, A. L., M.D. Stanford University Hospital, San Francisco, Calif. *Professor of Medicine.* (3, 1927; 4, 1927)
- Bloor, W. R., A.M., Ph.D. School of Medicine and Dentistry, University of Rochester, Rochester, N. Y. *Professor of Biochemistry.* (1, 1915; 2, 1910)
- Blum, Harold F., Ph.D. Naval Medical Research Institute, National Naval Medical Center, Bethesda, Md. *Principal Biophysicist.* (1, 1928)
- Blumberg, Harold, D.Sc. Research Laboratories, Winthrop Chemical Co., 33 Riverside Ave., Rensselaer, N. Y. *Research Biochemist.* (5, 1942)
- Blumenstock, Julius, M.D. Fort Sheridan Regional Hospital, Fort Sheridan, Ill. *Captain, Medical Corps.* (1, 1925)
- Blumgart, Hermann L., M.D. Beth Israel Hospital, 330 Brookline Ave., Boston, Mass. *Associate Professor of Medicine, Harvard Medical School; Lt. Col., M.C., Hdqtrs., 2nd Service Command, Governor's Island, N. Y.* (1, 1927)
- Blunt, Katharine, Ph.D., LL.D. 38 Glenwood Ave., New London, Conn. *President Emeritus, Connecticut College for Women.* (2, 1921)
- Boek, Joseph C., Ch.E., Ph.D. 2824 N. 46th St., Milwaukee 10, Wis. *Professor Emeritus of Biochemistry, Marquette Univ. Medical School; Biochemist, Milwaukee County Hospital.* (2, 1916)
- Bodansky, Aaron, Ph.D. Hospital for Joint Diseases, 1919 Madison Ave., New York City. *Biological Chemist.* (2, 1926)
- Bodansky, Oscar, M.D., Ph.D. Medical Research Laboratory, Edgewood Arsenal, Md. *Major, Medical Corps; Chief, Biochemistry Section, Medical Research Laboratory, Medical Division, Chemical Warfare Service.* (2, 1937; 3, 1942)
- Bodine, Joseph Hall, Ph.D. State University of Iowa, Iowa City. *Professor and Head of Department of Zoology.* (1, 1925)
- Boell, Edgar J., Ph.D. Osborn Zoological Laboratory, Yale University, New Haven, Conn. *Associate Professor of Biology.* (1, 1942)
- Bogert, L. Jean, Ph.D. Hotel Claremont, Berkeley, Calif. (2, 1917)
- Bogert, Marston Taylor, Se.D., LL.D., R.N.D. Columbia University, New York 27, N. Y. *Professor Emeritus of Organic Chemistry; Member, National Academy of Sciences.* (2, 1925)
- Bolliger, Adolph, Ph.D. Gordon Craig Research Laboratories, University of Sydney, Sydney, Australia. *Director of Research.* (2, 1928)
- Bollman, J. L., M.D. Mayo Clinic, Rochester, Minn. *Associate in Division of Experimental Surgery and Pathology, Mayo Clinic; Professor of Physiology, Mayo Foundation, University of Minnesota.* (4, 1927)
- Bond, Glenn C., Ph.D., M.D. The Upjohn Co., Research Laboratories, Kalamazoo, Mich. (6, 1939)
- Booker, Lela E., Ph.D. General Mills, Inc., Minneapolis, Minn. *Chief Nutritionist.* (2, 1933; 5, 1933)
- Bookman, Samuel, M.A., Ph.D. 624 Madison Ave., New York City. *Consulting Chemist, Mt. Sinai Hospital.* (2, 1912)
- Boor, Alden K., M.S., Ph.D. Department of Medicine, University of Chicago, Chicago, Ill. *Research Associate (Associate Prof.) of Biochemistry.* (2, 1931)
- Boothby, W. M., M.D., M.A., F.A.C.S., F.A.C.P., Metabolism Laboratory, The Mayo Clinic, Rochester, Minn. *Chief of Section of Clinical Metabolism in Division of Medicine, Mayo Clinic; Professor of Experimental Metabolism, Mayo Foundation, University of Minnesota; Chairman, Mayo Aero-Medical Unit; Member Subcommittee on Oxygen and Anoxia, N.R.C., O.S.R.D.* (1, 1915; 2, 1920; 3, 1923; 4, 1924)
- Bordley, James, III, M.D. Johns Hopkins Hospital, Baltimore, Md. *Associate Professor of Medicine, Johns Hopkins University.* (1, 1938)
- Borsook, Henry, M.D., Ph.D. California Institute of Technology, Pasadena 4. *Professor of Biochemistry.* (2, 1931)
- Bosworth, Alfred Willson, A.M., M.D. R. D. 4, Circleville, O. *Consulting Chemist.* (2, 1936; 5, 1935)
- Bott, Phyllis A., M.S., Ph.D. Woman's Medical College of Pennsylvania, East Falls, Philadelphia. *Associate Professor of Physiological Chemistry.* (2, 1938)
- Boucher, Robert V., M.A., Ph.D. 393 Frear Labs. State College, Pa. *Professor of Agricultural and Biological Chemistry.* (5, 1945)

- Bouman, H. D., M.D.\* Northwestern Univ. Med. School, 303 E. Chicago Ave., Chicago, Ill. Assistant Professor of Physical Medicine and Physiology. (1, 1943)
- Bourne, Wesley, M.D., C.M., M.Sc., F.R.C.P., D.A. (R.C.P. & S., Eng.). McGill University, Montreal, Canada. Lecturer in Anesthesia, Dept. of Pharmacology and Therapeutics. (3, 1936)
- Bourquin, Helen, M.S., Ph.D. 1331 N. Tejon St., Colorado Springs, Colo. (1, 1925)
- Bowman, Donald E., A.M., Ph.D. 6956 Warwick Rd., Indianapolis, Ind. Assistant Professor of Biochemistry, Indiana University School of Medicine. (2, 1944)
- Boyd, Eldon M., M.A., M.D., C.M. Queen's University, Kingston, Ontario, Canada. Professor and Head of the Department of Pharmacology. (3, 1941)
- Boyd, T. E., Ph.D. 706 S. Lincoln St., Chicago, Ill. Professor of Physiology, Loyola University, School of Medicine. (1, 1924)
- Boyd, William C., A.M., Ph.D. Boston University School of Medicine, 80 E. Concord St., Boston, Mass. Associate Professor of Biochemistry. (2, 1940; 6, 1933)
- Boyden, Edward A., A.M., Ph.D. University of Minnesota, Minneapolis. Professor of Anatomy and Chairman of the Department. (1, 1929)
- Boyer, Paul D., M.S., Ph.D. Division of Agric. Biochem., University of Minnesota, St. Paul. Assistant Professor. (2, 1944)
- Boyle, Paul E., D.M.D. School of Dentistry, University of Pennsylvania, 40th and Spruce Sts., Philadelphia 4. Professor of Oral Pathology. (4, 1939)
- Bozler, Emil, Ph.D. Ohio State University, Columbus. Associate Professor of Physiology. (1, 1932)
- Bradbury, James T., M.S., Sc.D. Dept. of Obstetrics and Gynecology, University Hospitals, Iowa City. Assistant Professor of Obstetrics and Gynecology. (1, 1941)
- Bradley, Harold C., Ph.D. Sherwood Hills, Madison, Wis. Professor of Physiological Chemistry, University of Wisconsin. (1, 1911; 2, 1908)
- Bradley, William B., Ph.D. American Institute of Baking, 1135 Fullerton Ave., Chicago, Ill. Director of the Laboratories. (1, 1939)
- Branch, Charles F., M.D. Children's Hospital, Boston, Mass. Director. (4, 1940)
- Branch, E. Arnold G., M.D. Bureau of Laboratories, General Hospital, St. John, N. B. Acting Director, Bureau of Laboratories, New Brunswick Department of Health. (4, 1929)
- Brand, Erwin, Ph.D. 630 W. 168th St., New York City. Associate Professor of Biological Chemistry, Columbia University. (2, 1929)
- Brandes, W. W., M.D. Roosevelt Hospital, W. 59th St., New York City. (4, 1931)
- Branham, Sara E., Ph.D., M.D., Sc.D. National Institute of Health, Bethesda, Md. Senior Bacteriologist. (6, 1926)
- Brannion, Hugh Douglas, M.A., Ph.D. 50 James St., Guelph, Canada. (5, 1933)
- Brassfield, Charles R., Ph.D. University of Michigan, Ann Arbor. Associate Professor of Physiology. (1, 1937)
- Bratton, Andrew Calvin, Jr., M.A., Ph.D. Research Laboratories, Parke, Davis and Co., Detroit 32, Mich. Director of Pharmacological Research. (3, 1941)
- Braun, Herbert A., Ph.D. Food & Drug Administration, Federal Security Agency, Washington, D. C. Associate Pharmacologist. (3, 1941)
- Brewer, George, M.D. University of Pennsylvania, School of Medicine, Philadelphia. Assistant Professor of Physiology. (1, 1937)
- Bridge, Edward M., M.D. 219 Bryant St., Buffalo, N. Y. Research Professor, Department of Pediatrics, Univ. of Buffalo. (2, 1940)
- Briggs, A. P., M.D. University of Georgia, Augusta. Associate Professor in Biochemistry and Medicine. (2, 1923)
- Brink, Frank, Jr., Ph.D. Johnson Research Foundation, University of Pennsylvania, Philadelphia. Fellow in Medical Physics, Johnson Research Foundation; Lecturer in Biophysics, Graduate School, University of Pennsylvania. (1, 1942)
- Brinkhous, K. M., M.D. State University of Iowa, Department of Pathology, Medical Laboratories Building, Iowa City. Associate Professor of Pathology. (4, 1939)
- Britton, Sydney W., M.D. University of Virginia School of Medicine, University. Professor of Physiology. (1, 1925)
- Brobeck, John R., M.D., Ph.D.\* Yale University School of Medicine, New Haven, Conn. Instructor, Laboratory of Physiology. (1, 1943)
- Brodie, Bernard B., Ph.D. New York University College of Medicine, 477 First Ave., New York 16, N. Y. Assistant Professor of Pharmacology. Also: Third (NYU) Medical Division, Goldwater Memorial Hospital, Welfare Island 17, New York. Research Associate in Biochemistry. (2, 1940; 3, 1945)
- Brody, Samuel, M.A., Ph.D. Dairy Building, University of Missouri, Columbia. Associate Professor, College of Agriculture and Agricultural Experiment Station. (2, 1929; 5, 1933)
- Bronfenbrenner, J. J., Ph.D., D.P.H. Washington University School of Medicine, St. Louis, Mo. Professor of Bacteriology and Immunology. (4, 1940; 6, 1918)
- Bronk, Detlev W., M.S., Ph.D., Sc.D. The Elbridge Reeves Johnson Foundation for Medical

- Physics, University of Pennsylvania, Philadelphia. *Johnson Professor of Biophysics and Director, Johnson Foundation; Member National Academy of Sciences.* (1, 1927)
- Brookes, Margaret C. Hessler, A.M., Ph.D. University of Chicago, Chicago, Ill. *Assistant Professor, Department of Home Economics.* (5, 1935)
- Brooks, Chandler McCuskey, M.A., Ph.D. Johns Hopkins University School of Medicine, Baltimore, Md. *Associate Professor of Physiology.* (1, 1934)
- Brooks, Clyde, Ph.D., M.D., LL.D. Essex College of Med. and Surg., Broad St. at 3rd Ave., Newark 4, N.J. (1, 1910; 3, 1912)
- Brooks, Matilda Moldenhauer, M.S., Ph.D. Department of Zoology, University of California, Berkeley. *Research Associate in Biology.* (1, 1923)
- Brooks, Sumner Cushing, Ph.D. University of California, Berkeley. *Professor of Zoology.* (1, 1923)
- Brown, Goronwy Owen, M.D. 1325 S. Grand Blvd., St. Louis, Mo. *Professor of Internal Medicine, St. Louis University.* (4, 1927)
- Brown, Claude P., M.D. 1930 Chestnut St., Philadelphia, Pa. *Assistant Director, Pennsylvania State Board of Health Laboratories.* (6, 1913)
- Brown, Dugald E. S., M.A., Ph.D. New York University College of Dentistry, 209 E. 23rd St., New York City. *Professor of Physiology.* (1, 1932)
- Brown, Edgar D., Pharm.D., M.D. Paynesville, Minn. *Associate Professor of Pharmacology Emeritus.* (1, 1907; 3, 1909)
- Brown, Frank A., Jr., M.A., Ph.D. Zoological Laboratories, Northwestern University, Evanston, Ill. *Associate Professor of Zoology.* (1, 1940)
- Brown, John B., M.S., Ph.D. Ohio State University, Columbus. *Professor of Physiological Chemistry.* (2, 1927; 5, 1934)
- Brown, Rachel, M.S., Ph.D. 26 Buckingham Drive, Albany, N. Y. *Senior Biochemist, Division of Laboratories and Research, New York State Department of Health.* (6, 1933)
- Brown, Robert V., Ph.D.\* University of North Dakota, Grand Forks. *Professor of Physiology and Pharmacology.* (1, 1945)
- Browne, J. S. L., M.D., Ph.D., F.R.S.C. University Clinic, Royal Victoria Hospital, Montreal, Canada. *Assistant Professor of Medicine, McGill University.* (1, 1934)
- Brownell, Katharine A., M.A., Ph.D.\* Department of Physiology, Ohio State University, Columbus. *Research Associate.* (1, 1943)
- Brues, Austin M., M.D. P.O. Box 5207, Chicago 80, Ill. *Assistant Professor of Medicine, Harvard Medical School; Assistant Physician, Mass. General Hospital.* (1, 1940)
- Bruger, Maurice, M.D., C.M., M.Sc. 245 E. 17th St., New York 3, N. Y. *Associate Clinical Professor of Medicine, New York Post-Graduate Medical School of Columbia University; Chief, Division of Pathological Chemistry, New York Post-Graduate Hospital.* (2, 1935; 5, 1935)
- Bruhn, John M., Ph.D. Department of Physiology, Medical College of Alabama, 620 South 20th St., Birmingham 5. (1, 1939)
- Bruner, Harry Davis, M.S., M.D., Ph.D. University of Pennsylvania School of Medicine, Philadelphia 4. *Associate in Pharmacology.* (3, 1945)
- Brunsehwig, Alexander, M.D. University of Chicago, Chicago, Ill. *Professor of Surgery.* (4, 1937)
- Bryan, W. Ray, Ph.D. 5614 Glenwood Rd., Bethesda, Md. *Senior Biologist, National Cancer Institute.* (1, 1934; 4, 1940)
- Buchanan, J. William, Ph.D. Northwestern University, Evanston, Ill. *Professor of Zoology.* (1, 1927)
- Buehbinder, Leon, Ph.D. Department of Health, 125 Worth St., New York City. (6, 1934)
- Buehbinder, William C., M.S., M.D. 104 S. Michigan Ave., Chicago, Ill. *Assistant Professor of Medicine, Northwestern University Medical School; Associate in Medicine, Michael Reese Hospital.* (1, 1940)
- Buckner, G. Davis, Ph.D. Kentucky Agricultural Experiment Station, Lexington. *In Charge of Animal Nutrition.* (2, 1920)
- Bucy, Paul C., M.S., M.D. 25 E. Washington St., Chicago, Ill. *Professor of Neurology and Neurological Surgery, University of Illinois.* (1, 1933)
- Buddingh, G. John, M.D. Vanderbilt University School of Medicine, Nashville, Tenn. *Associate Professor of Bacteriology.* (4, 1940)
- Buell, Mary V., Ph.D. 115 Ely Place, Madison 5, Wis. (2, 1921)
- Bugbee, Edwin P., M.D. 131 N. Norwinden St., Springfield, Pa. (1, 1928)
- Bugher, John C., M.D. Rockefeller Foundation, 49 W. 49th St., New York 20. *Member of Staff International Health Division of the Rockefeller Foundation.* (4, 1935)
- Bukantz, Samuel C., M.D. 1955 Grand Concourse, Bronx 53, N. Y. (6, 1943)
- Bulatao, Emilio, M.D. University of the Philippines, Manila, P.I. *Professor of Physiology.* (1, 1924)
- Bulger, Harold A., Ph.D., M.D. Barnes Hospital, 600 S. Kingshighway, St. Louis, Mo. *Assistant Professor of Medicine, Washington University.* (5, 1933)
- Bull, Henry B., Ph.D. Northwestern University Medical School, 303 E. Chicago Ave., Chicago,

- Ill. Associate Professor, Department of Chemistry. (2, 1937)
- Bunde, Carl A., M.A., Ph.D.\* Southwestern Medical Foundation, Dallas, Texas. Associate Professor of Physiology and Pharmacology. (1, 1943)
- Bunney, William E., Ph.D. E. R. Squibb & Sons, New Brunswick, N. J. Director of Biologic Products Production. (6, 1931)
- Bunting, Charles H., M.D. 139 Armory St., Hamden, Conn. Emeritus Professor of Pathology, University of Wisconsin. (4, 1913)
- Bunzell, H. H., Ph.D. Box 44, General Post Office, New York 1, N. Y. Director, Bunzell Laboratories. (2, 1908)
- Burchell, Howard B., M.D., Ph.D. 799 3rd St., S.W., Rochester, Minn. Instructor in Medicine, Mayo Foundation, Graduate School, University of Minnesota; Consultant in Medicine, Mayo Clinic, Rochester, Minn. (1, 1942)
- Burdick, H. O., M.A., Sc.D. (hon.). Alfred University, Alfred, N. Y. Professor of Biology. (1, 1940)
- Burdon, Kenneth L., Sc.M., Ph.D. Baylor University College of Medicine, Houston, Texas. Professor of Bacteriology; Consultant, United States Public Health Service. (6, 1936)
- Burge, W. E., A.M., Ph.D. University of Illinois, Urbana. Associate Professor of Physiology. (1, 1911)
- Burk, Dean, Ph.D. National Cancer Institute, U. S. Public Health Service, Bethesda, Md. Senior Chemist. (2, 1939)
- Burky, Earl L., M.S., M.D. Johns Hopkins Hospital, Baltimore, Md. Associate Professor of Ophthalmology, Wilmer Institute of Ophthalmology, Johns Hopkins University. (6, 1931)
- Burnett, Theo. C., M.D. Box 216, Carmel, Calif. Associate Professor of Physiology Emeritus, University of California, Berkeley. (1, 1911)
- Burns, Edward L., M.D. Louisiana State University, School of Medicine, New Orleans. Associate Professor of Pathology and Bacteriology. (4, 1939)
- Burr, George O., M.A., Ph.D., LL.D. University of Minnesota, Minneapolis. Director, Division of Physiological Chemistry. (2, 1928; 5, 1933)
- Burrill, Marie Wecker, Ph.D.\* 1415 Hudson Ave., Chicago 10, Ill. Instructor in Physiology, Northwestern University Medical School. (1, 1944)
- Burrows, Montrose T., M.D. 201 N. El Molino Ave., Pasadena, Calif. (4, prior to 1920)
- Burton, Alan C., Ph.D. Department of Medical Research, University of Western Ontario, London, Canada. Assistant Professor of Medical Research. (1, 1937)
- Burton-Opitz, Russell, M.S., M.D., Ph.D. 218 Bridle Way, Palisade, N. J. Attending Cardiologist, Lenox Hill Hospital; Attending Physician,
- Cumberland Hospital; Consulting Cardiologist, Englewood, North Hudson, Holy Name and Hackensack Hospitals. (1, 1902; 2, 1906; 3, 1919)
- Bush, Milton T., Ph.D. Vanderbilt University School of Medicine, Nashville, Tenn. Research Associate in Pharmacology. (3, 1938)
- Butler, Thomas C., M.D. Vanderbilt University School of Medicine, Nashville, Tenn. Assistant Professor of Pharmacology. (3, 1938)
- Butt, Hugh R., M.D. U. S. Naval Hospital, Corona, Calif. (5, 1942)
- Butts, Joseph S., M.S., Ph.D. Hq. A.A.F., Pentagon Bldg., Washington, D. C. On leave to U. S. Army (Major). (2, 1936)
- Butz, Eleanor W. J., Ph.D. Beltsville, Md. Collaborator, Div. Animal Husbandry, U. S. D. A., Beltsville Research Center. (6, 1935)
- Cahill, William M., Ph.D. 5532 Marlborough St., Detroit, Mich. Consulting Biochemist. (2, 1940)
- Cajori, Florian A., Ph.D. University of Pennsylvania School of Medicine, Philadelphia 4. On leave to U. S. Army (Major). (2, 1922; 5, 1933)
- Caldwell, Mary L., A.M., Ph.D. Department of Chemistry, Columbia University, New York City. Associate Professor of Chemistry. (2, 1924; 5, 1933)
- Calloway, Nathaniel Oglesby, Ph.D., M.D. Medical School, University of Illinois, 1819 Polk St., Chicago 12. Assistant in Medicine. (3, 1945)
- Calvin, D. Bailey, M.A., Ph.D. School of Medicine, University of Texas, Galveston. Professor, Biological Chemistry; Associate Dean, School of Medicine. (1, 1934; 2, 1939)
- Cameron, A. T., M.A., D.Sc., F.I.C., F.R.S.C. Medical College, Winnipeg, Manitoba, Canada. Professor of Biochemistry, Faculty of Medicine, University of Manitoba; Biochemist, Winnipeg General Hospital. (1, 1914; 2, 1914)
- Camp, Walter J. R., M.D., Ph.D. 1853 Polk St., Chicago, Ill. Professor of Pharmacology and Therapeutics, University of Illinois. (3, 1926)
- Campbell, Berry, Ph.D.\* University of Minnesota, Minneapolis 14. Assistant Professor of Anatomy. (1, 1945)
- Campbell, Dan H., M.S., Ph.D. Department of Chemistry, California Institute of Technology, Pasadena, Calif. Assistant Professor of Immunochemistry. (6, 1938)
- Campbell, H. Louise, Ph.D. 435 W. 119th St., Apt. 9-F, New York City. Research Assistant in Food Chemistry, Columbia University. (5, 1933)
- Campbell, James, M.A., Ph.D.\* University of Toronto, Toronto, Ontario, Canada. Assistant Professor of Physiology. Lieutenant Commander, (S.B.) R.C.N.V.R. (1, 1943)

- Campbell, Walter Ruggles, M.A., M.D., F.R.C.P. (C), F.R.S.C. 69 Madison Ave., Toronto, Canada. Assistant Professor of Medicine and Clinical Medicine, University of Toronto; Assistant Physician, Toronto General Hospital. (2, 1922)
- Cannan, R. Keith, D.Sc. 477 First Ave., New York City. Professor of Chemistry, New York University College of Medicine. (2, 1931)
- Cannon, Paul R., M.D., Ph.D. University of Chicago, Chicago, Ill. Professor of Pathology. (4, 1930; 6, 1929)
- Cantarow, Abraham, M.D. Jefferson Medical College, Philadelphia 7, Pa. Professor of Physiological Chemistry. (1, 1932; 3, 1935)
- Cantoni, G. L., M.D. Long Island College of Medicine, 350 Henry St., Brooklyn 2, N. Y. Assistant Professor of Physiology and Pharmacology. (3, 1945)
- Canzanelli, Attilio, M.D. Tufts College Medical School, 416 Huntington Ave., Boston, Mass. Associate Professor in the Department of Physiology. (1, 1934)
- Carlson, A. J., A.M., Ph.D., M.D., LL.D. Hull Physiological Laboratory, University of Chicago, Chicago, Ill. Professor of Physiology Emeritus; Member of the National Academy of Sciences. (1, 1904; 5, 1933)
- Carlson, Loren D., Ph.D.\* Dept. of Animal Biology, Univ. of Washington, Seattle 5. (1, 1945)
- Carmichael, Emmett B., Ph.D. The Medical College of Alabama, Department of Biochemistry, Birmingham 5. Professor. (1, 1931)
- Carmichael, Leonard, Ph.D., Sc.D., Litt.D., LL.D. Tufts College, Medford, Mass. Director, the Tufts College Research Laboratory of Sensory Psychology and Physiology and President of the College. (1, 1937)
- Carpenter, Thorne M., Ph.D. 159 Corey St., West Roxbury 32, Mass. Director, Nutrition Laboratory of the Carnegie Institution of Washington. (1, 1915; 2, 1909; 5, 1935)
- Carr, C. Jelless, Ph.D. School of Medicine, University of Maryland, Baltimore. Associate Professor of Pharmacology. (3, 1940)
- Carr, Jesse L., M.D. University of California Medical School, Third and Parnassus Aves., San Francisco. Assistant Professor of Pathology. (4, 1940)
- Carter, Herbert E., M.A., Ph.D. 452 Noyes Laboratory, Urbana, Ill. Professor of Biochemistry, University of Illinois. (2, 1937; 5, 1941)
- Cartland, George F., M.S., Ph.D. The Upjohn Co., Research Dept., Kalamazoo, Mich. Head, Antibiotics Research. (2, 1936)
- Cary, Charles A., S.B. Dairy Research Laboratory, Beltsville, Md. Chief, Division of Nutrition and Physiology, Bureau of Dairy Industry; U. S. Department of Agriculture. (2, 1920)
- Casey, Albert Eugene, M.D. Jefferson and Baptist Hospitals, Birmingham, Ala. Pathologist (4, 1933)
- Cash, James Robert, M.D. University Hospital, Charlottesville, Va. Professor of Pathology, University of Virginia. (4, 1924)
- Castle, Edward S., M.A., Ph.D. Biological Laboratories, Harvard University, Divinity Ave., Cambridge, Mass. Assistant Professor of General Physiology. (1, 1934)
- Castle, William B., M.D., S.M. (Hon. Yale), M.D. (Hon. Utrecht). Boston City Hospital, Boston, Mass. Professor of Medicine, Harvard Medical School; Associate Director, Thorndike Memorial Laboratory and Director, II and IV Medical Services (Harvard), Boston City Hospital. (4, 1942)
- Catchpole, Hubert Ralph, Ph.D. National Naval Medical Center, Bethesda, Md. Ensign, USNR; Research Assistant in Physiology (Assistant Professor), Yale University Medical School. (1, 1941)
- Cathcart, E. P., M.D., D.Sc., LL.D. University of Glasgow, Glasgow, Scotland. Dean of University. (5, 1935)
- Catron, Lloyd, M.D. The City Hospital, Akron, O. Pathologist. (4, 1939)
- Cattell, McKeen, A.M., Ph.D., M.D. Cornell University Medical College, 1300 York Ave., New York City. Professor of Pharmacology. (1, 1923; 3, 1924)
- Cerecedo, Leopold R., Ph.D. Fordham University, New York City. Professor of Biochemistry. (2, 1931; 5, 1945)
- Chadwick, Leigh Edward, Ph.D.\* Medical Research Laboratory, Edgewood Arsenal, Md. (1, 1944)
- Chaikoff, I. L., A.M., Ph.D., M.D. University of California, Berkeley. Associate Professor of Physiology. (1, 1932)
- Chalkley, Harold W., A.M., Ph.D. U. S. Public Health Service, National Institute of Health, Bethesda, Md. Senior Physiologist. (1, 1932)
- Chambers, Leslie Addison, M.S., Ph.D. Johnson Foundation for Medical Physics, University of Pennsylvania, Philadelphia. Lecturer in Biophysics; Associate in Medical Physics; Associate in Pediatrics. (1, 1940)
- Chambers, Robert, A.M., Ph.D. New York University, Washington Square East, New York City. Research Professor of Biology. (1, 1932)
- Chambers, William H., M.S., Ph.D. Cornell University Medical College, 1300 York Ave., New York City. Associate Professor of Physiology. Major, S.N.C. A U.S. (1, 1924; 5, 1933)
- Chandler, Caroline A., M.D. Mass. Dept. of Public Health Service, 73 Tremont St., Boston. Supervisor of Clinics for Crippled Children. (6, 1938)

- Chandler, Joseph P., M.S., Ph.D. Cornell University Medical College, 1300 York Ave., New York City. *Assistant Professor of Biochemistry.* (2, 1944; 5, 1944)
- Chanutin, Alfred, Ph.D. Box 1038 (University Station), Charlottesville, Va. *Professor of Biochemistry, University of Virginia.* (2, 1925)
- Chapman, C. W., M.Sc., Ph.D. University of Maryland, Baltimore. *Professor of Pharmacology.* (3, 1932)
- Chargaff, Erwin, Ph.D. Columbia University, College of Physicians and Surgeons, 630 W. 168th St., New York City. *Assistant Professor of Biological Chemistry.* (2, 1935)
- Charipper, Harry Adolph, M.S., Ph.D. Washington Square College of Arts and Sciences, 100 Washington Square East, New York City. *Professor of Biology and Chairman of the Department.* (1, 1941)
- Chase, Aurin M., A.M., Ph.D. Department of Biology, Princeton University, Princeton, N. J. *Research Associate.* (1, 1939)
- Chase, Harold F., M.D. Western Reserve University School of Medicine, Cleveland, O. *Assistant Professor of Pharmacology.* (3, 1944)
- Chase, Merrill W., M.S., Ph.D. Rockefeller Institute, 66th St. and York Ave., New York City. *Member of Staff.* (6, 1938)
- Chasis, Herbert, M.D., Med. Sc.D. 44 E. 67th St., New York City. *Assistant Professor of Medicine, New York University, College of Medicine.* (1, 1941)
- Chatfield, Charlotte, B.S. Civilian Food Requirement Branch, Office of Marketing Services, War Food Administration, Washington 25, D. C. *In Charge, Food Composition Section, Bureau of Home Economics.* (5, 1941)
- Chen, Graham, Sc.D., M.D. Dept. of Pharmacology, University of Chicago, Chicago, Ill. *Research Associate (Assistant Prof.).* (3, 1944)
- Chen, K. K., Ph.D., M.D. The Lilly Research Laboratories, Indianapolis, Ind. *Director of Pharmacological Research; Professor of Pharmacology, Indiana University School of Medicine, Indianapolis.* (1, 1929; 3, 1942)
- Cheney, Ralph H., A.M., M.S., Sc.D. Long Island University, 600 Lafayette Ave., Brooklyn, N. Y. *Chairman, Biology Department.* (3, 1934)
- Chenoweth, Maynard Burton, M.D. Medical Research Laboratory, Edgewood Arsenal, Md. Capt., M.C., AUS, *Pharmacology Section.* (3, 1945)
- Chesnyc, Alan M., M.D. The Johns Hopkins Hospital, Baltimore, Md. *Dean, Johns Hopkins Medical School; Associate Professor of Medicine.* (4, 1925)
- Child, Charles Manning, Ph.D., D.Sc. (hon.). Jordan Hall, Stanford University, Calif. *Member,*
- National Academy of Sciences; Professor Emeritus, University of Chicago.* (1, 1923)
- Chow, Bacon F., Ph.D. Squibb Institute for Medical Research, New Brunswick, N. J. *Head of the Department of Physical Chemistry.* (2, 1940; 6, 1944)
- Christensen, L. Royal, Ph.D. New York University College of Medicine, 477 First Ave., New York City. *Medical Fellow, National Research Council.* (6, 1942)
- Christian, Henry A., M.D. 20 Chapel St., Brookline, Mass. *Hershey Professor of the Theory and Practice of Physic, Emeritus, Harvard University, recalled to active teaching; Clinical Professor of Medicine, Tufts College Medical School; Physician-in-Chief, Peter Bent Brigham Hospital, Boston; Visiting Physician, Beth Israel Hospital, Boston.* (4, 1924)
- Christman, Adam A., Ph.D. University of Michigan Medical School, Ann Arbor. *Associate Professor of Biological Chemistry.* (2, 1929)
- Chu, Wei-chang, M.D. Dept. Pharmacology and Therapeutics, Stanford University Medical School, 2398 Sacramento St., San Francisco 15, Calif. *Acting Instructor in Pharmacology.* (3, 1945)
- Clark, Ada R., M.A., Ph.D. College of Physicians and Surgeons, 630 W. 168th St., New York City. *Instructor in Bacteriology.* (6, 1936)
- Clark, Byron B., M.S., Ph.D. Albany Medical College, Albany, N. Y. *Associate Professor of Physiology and Pharmacology.* (3, 1940)
- Clark, Eliot R., M.D. University of Pennsylvania, Philadelphia. *Professor and Head of Department of Anatomy.* (1, 1919)
- Clark, Ernest D., A.M., Ph.D. 826 Skinner Bldg., Seattle 1, Wash. *Director of the Laboratories, Northwest Branch, National Canners' Association.* (2, 1912)
- Clark, George, Ph.D.\* Yerkes Laboratory of Primate Biology, Orange Park, Fla. *Assistant Professor of Psychobiology.* (1, 1943)
- Clark, Guy W., A.M., Ph.D. c/o Lederle Laboratories, Inc., Pearl River, N. Y. *Technical Director.* (2, 1922)
- Clark, Janet Howell, A.M., Ph.D. Anderson Hall, University of Rochester, Rochester, N. Y. *Dean of the College for Women and Professor in the Division of Biological Sciences.* (1, 1922)
- Clark, Paul F., Ph.D. University of Wisconsin Medical School, Madison. *Professor of Bacteriology.* (4, 1923; 6, 1928)
- Clark, William G., Ph.D. Department of Aviation Medicine, University of Southern California, Los Angeles 7. (1, 1942)
- Clark, William Mansfield, M.A., Ph.D., D.Sc. Johns Hopkins University, Baltimore, Md. *Professor of Physiological Chemistry; Member, National Academy of Sciences.* (2, 1920)

- Clarke, Hans Thacher, D.Sc. (London), F.I.C. 630 W. 168th St., New York City. Professor of Biological Chemistry, Columbia University, College of Physicians and Surgeons. (2, 1929)
- Clarke, Robert W., Ph.D. Yale University School of Medicine, 333 Cedar St., New Haven, Conn. Instructor in Physiology. (1, 1936)
- Clausen, Samuel Wolcott, M.D. Strong Memorial Hospital, Rochester, N. Y. Professor of Pediatrics, School of Medicine, University of Rochester. (2, 1922)
- Cleghorn, Robert Allen, M.D., D.Sc. (Aberdeen). Department of Medicine, University of Toronto, Toronto, Ont., Canada. Junior Demonstrator in Medicine; Junior Assistant Attending Physician, Toronto General Hospital. (1, 1937)
- Climenko, David Robert, M.D., Ph.D. Winthrop Chemical Co., 33 Riverside Ave., Rensselaer, N. Y. Pharmacologist; Associate in Biochemistry and Instructor in Medicine, Albany Medical College. (1, 1933)
- Clowes, George Henry Alexander, Ph.D., D.Sc. (hon.), LL.D. (hon.). Eli Lilly & Co., Indianapolis, Ind. Director of Research. (2, 1914; 6, 1919)
- Coca, Arthur F., A.M., M.D. Pearl River, N. Y. Medical Director, Lederle Laboratories. (6, 1916)
- Code, Charles F., Ph.D., M.D. Mayo Foundation, Rochester, Minn. Professor of Physiology. (1, 1939)
- Coffey, Julia M., A.B. Division of Laboratories & Research, New York State Department of Health, Albany, N. Y. Associate Bacteriologist. (6, 1937)
- Coghill, Robert D., M.S., Ph.D. Northern Regional Research Laboratory, U. S. Department of Agriculture, Peoria, Ill. Chief, Fermentation Division. (2, 1932)
- Cohen, Barnett, M.S., Ph.D. Johns Hopkins University School of Medicine, 710 N. Washington St., Baltimore 5, Md. Associate Professor of Physiological Chemistry. (2, 1935)
- Cohen, Milton B., M.D. 10616 Euclid Ave., Cleveland, O. Director, The Asthma, Hay Fever and Allergy Foundation. (6, 1931)
- Cohen, Philip P., Ph.D., M.D. Service Memorial Institute, University of Wisconsin, Madison. Associate Professor of Physiological Chemistry. (2, 1941)
- Cohen, Sophia M., B.S. Division of Laboratories and Research, New York State Department of Health, Albany, N. Y. Assistant Bacteriologist. (6, 1938)
- Cohn, Alfred E., M.D. 300 Central Park W., New York City. Member, Rockefeller Institute for Medical Research. (1, 1911; 3, 1913)
- Cohn, Edwin J., Ph.D., A.M. (Hon.), Sc.D. (Hon.). 183 Brattle St., Cambridge, Mass. Professor of Biological Chemistry, Harvard Medical School, Boston; Member, National Academy of Sciences. (1, 1919; 2, 1919)
- Cohn, Waldo E., M.S., Ph.D. 109 Marion Rd., Oak Ridge, Tenn. Senior Biochemist, Clinton Laboratories, Knoxville, Tenn. (2, 1944)
- Cole, Arthur G., Ph.D. 1853 W. Polk St., Chicago 12, Ill. Assistant Professor of Biological Chemistry, University of Illinois College of Medicine. (2, 1930)
- Cole, Harold N., M.D. 1352 Hanna Bldg., Cleveland, O. Clinical Professor of Dermatology and Syphilology, Western Reserve University. (3, 1925)
- Cole, Kenneth S., Ph.D. 5618 Kimbark Ave., Chicago, Ill. (1, 1934)
- Cole, Rufus, M.D., D.Sc. Mount Kisco, N. Y. Member Emeritus, Rockefeller Institute for Medical Research. (4, 1924; 6, 1917)
- Cole, Versa V., Ph.D., M.D. Indiana University School of Medicine, 1040-1232 West Michigan St., Indianapolis. Assistant Professor of Pharmacology. (3, 1941)
- Collett, Mary Elizabeth, A.M., Ph.D. Mather College, Western Reserve University, Cleveland, O. Associate Professor of Biology. (1, 1921)
- Collier, H. Bruce, M.A., Ph.D. Dalhousie University, Halifax, N. S. Associate Professor of Biochemistry. (2, 1944)
- Collings, William Doyne, Ph.D.\* University of Texas School of Medicine, Galveston. Assistant Professor of Physiology. (1, 1944)
- Collins, Dean A., M.A., Ph.D., M.D. Temple Univ. School of Medicine, 3400 N. Broad St., Philadelphia 40, Pa. (1, 1938)
- Collins, Russell J., A.M., M.D., F.R.C.P. (Can.) M.R.C.P. (Edin.) F.A.C.P. St. John, New Brunswick, Canada. Medical Superintendent of St. John Tuberculosis Hospital. (3, 1915)
- Collip, J. B., A.M., Ph.D., D.Sc., M.D., C.B.E. McGill University, Montreal, Quebec, Canada. Director, Research Institute of Endocrinology. (1, 1920; 2, 1920)
- Colowick, Sidney P., Ph.D. Washington University Medical School, Euclid and Scott Aves., St. Louis, Mo. Assistant Professor of Pharmacology. (2, 1944)
- Coman, Dale R., M.D. McManes Laboratory of Pathology, University of Pennsylvania School of Medicine, Philadelphia. Assistant Professor of Pathology. (4, 1939)
- Comroe, Julius H., Jr., M.D.\* University of Pennsylvania Medical School, Philadelphia. Assistant Professor of Pharmacology. (1, 1943; 3, 1939)

- Conant, James B., Ph.D. 5 University Hall, Cambridge, Mass. President, Harvard University; Member, National Academy of Sciences. (2, 1932)
- Concepcion, Isabolo, M.D. College of Medicine and Surgery, Manila, P.I. Professor of Physiology, University of the Philippines. (1, 1919)
- Conklin, Ruth E., M.S., Ph.D. Vassar College. Poughkeepsie, N. Y. Professor of Physiology. (1, 1940)
- Conn, Jerome W., M.D. University Hospital, Ann Arbor, Mich. Assistant Professor of Internal Medicine and Research Associate in Nutrition. (5, 1942)
- Cook, Donald Hunter, Ph.D. Department of Chemistry, University of Florida, Coral Gables 31. (2, 1929)
- Cooke, Robert A., A.M., Sc.D. (hon.), M.D. 60 E. 58th St., New York City. Director, Department of Allergy, Roosevelt Hospital. (6, 1920)
- Coolidge, Thomas B., M.D., Ph.D. Abbot Hall, University of Chicago, Chicago 37, Ill. Associate Professor of Biochemistry and Walter G. Zoller Memorial Dental Clinic. (2, 1942)
- Coon, Julius M., Ph.D. University of Chicago, Chicago, Ill. Instructor in Pharmacology. (3, 1941)
- Coons, Callie Mae, Ph.D. Box 164, Washington 4, D. C. (5, 1933)
- Cope, Otis M., M.D. New York Medical College, Flower and Fifth Avenue Hospitals, Fifth Ave. at 106th St., New York City. Professor of Physiology and Biochemistry. (1, 1929)
- Corbin, Kendall B., M.D. University of Tennessee College of Medicine, 875 Monroe, Memphis. Professor of Anatomy. (1, 1941)
- Corcoran, Arthur Curtis, C.M., M.D. Cleveland Clinic Foundation, Cleveland 6, O. (1, 1940)
- Corey, Edward Lyman, Ph.D. School of Medicine, University of Virginia, University. Assistant Professor of Physiology. (1, 1931)
- Cori, Carl F., M.D. Washington University School of Medicine, Kingshighway and Euclid Ave., St. Louis, Mo. Professor of Pharmacology and Biochemistry; Member, National Academy of Sciences. (2, 1925; 3, 1934)
- Cori, Gerty T., M.D. Washington University School of Medicine, St. Louis, Mo. Research Associate Professor in Pharmacology and Biochemistry. (2, 1927; 3, 1934)
- Corley, Ralph Conner, Ph.D. Department of Chemistry, Purdue University, Lafayette, Ind. Professor of Biochemistry. (2, 1927)
- Cornwall, Leon, M.D. 55 E. 76th St., New York City. Attending Neurologist, N. Y. Neurological Institute. (6, 1920)
- Corper, Harry J., M.D., Ph.D. 1295 Clermont St., Denver, Colo. Director of Research, National Jewish Hospital. (2, 1912)
- Corson, Samuel A., M.S., Ph.D.\* Department of Physiology, University of Minnesota School of Medicine, Minneapolis. Instructor in Physiology. (1, 1943)
- Corwin, Warren C., M.D. 1833 Girard Avenue So., Minneapolis 2, Minn. Major, M.C., A U.S. (4, 1940)
- Co Tui, Frank, M.D. New York University College of Medicine, 477 First Ave., New York City. Associate Professor of Experimental Surgery. (3, 1931)
- Cournand, André Frederic, M.D.\* Chest Service, Bellevue Hospital, CD Building, 1st Ave. at 28th St., New York City. Assistant Professor of Medicine, College of Physicians and Surgeons, Columbia University. (1, 1944)
- Cowgill, George Raymond, Ph.D. 333 Cedar St., New Haven, Conn. Professor of Nutrition, Yale University. (1, 1923; 2, 1922; 5, 1933)
- Cox, Gerald J., M.S., Ph.D. 200 S. 7th Ave., LaGrange, Ill. Research Group Leader, Corn Products Refining Co. (2, 1930; 5, 1935)
- Cox, Warren M., Jr., Ph.D. Mead Johnson & Co., Evansville, Ind. Director of Nutritional Research. (2, 1935; 5, 1945)
- Craig, L. C., M.S., Ph.D. Rockefeller Institute, 66th St. and York Ave., New York City. Associate in Chemical Pharmacology. (2, 1938)
- Crampton, E. W., Ph.D. Maedonald College, Quebec, Canada. Associate Professor of Animal Nutrition. (5, 1940)
- Crandall, Lathan A., Jr., M.D., Ph.D. University of Tennessee College of Medicine, Memphis. Professor of Physiology. (1, 1930; 5, 1940)
- Cressy, Norman L., M.D. Respiratory Disease Commission Laboratory, Station Hospital, Section 2, Fort Bragg, N. C. Capt., M. C., U. S. A.; Member Commission on Acute Respiratory Diseases. (6, 1943)
- Gretcher, Leonard H., Ph.D. Mellon Institute of Industrial Research, University of Pittsburgh, Pittsburgh, Pa. Assistant Director and Head of the Department of Research in Pure Chemistry. (2, 1930)
- Crider, Joseph O., M.D. Jefferson Medical College, Philadelphia, Pa. Associate Professor of Physiology and Assistant Dean. (1, 1935)
- Crisler, George R., Ph.D., M.D. V. A. A. F., Victorville, Calif. Captain, Medical Corps. (1, 1930)
- Crismon, Jefferson Martineau, M.D.\* Stanford University, Calif. Assistant Professor of Physiology. (1, 1944)
- Crittenden, Phoebe J., M.S., Ph.D. Merck Institute for Therapeutic Research, Rahway, N. J. Associate Physiologist. (1, 1937; 3, 1937)

- Cromwell, Hobart W., Sc.D. Abbott Laboratories, North Chicago, Ill. *Bacteriologist.* (6, 1929)
- Crozier, William J., Ph.D. Biological Laboratories, Harvard University, Cambridge, Mass. *Professor of General Physiology.* (1, 1928)
- Cruickschank, Ernest W. H., M.D., D.Sc., Ph.D. M.R.C.P., F.R.S.E. Marischal College, University of Aberdeen, Aberdeen, Scotland. *Professor of Physiology.* (1, 1931)
- Csonka, F. A., Ph.D. Bureau of Human Nutrition and Home Economics, U. S. Department of Agriculture, Beltsville, Md. *Senior Chemist.* (2, 1924)
- Cullen, Stuart C., M.D. University Hospitals, Iowa City, Iowa. *Assistant Professor of Surgery-Anesthesia.* (3, 1944)
- Culler, Elmer A. K., Ph.D. University of Rochester, Rochester, N. Y. *Professor of Psychology and Director of the Laboratory.* (1, 1936)
- Cunningham, Raymond W., M.S., Ph.D. Lederle Laboratories, Inc., Pearl River, N. Y. *Head, Pharmacology Research.* (3, 1941)
- Cunningham, Robert Sydney, A.M., M.D., Sc.D. Albany Medical College, Albany, N. Y. *Professor of Anatomy and Dean.* (1, 1923)
- Curnen, Edward C., M.D. Hospital of Rockefeller Institute, 66th St. and York Ave., New York City. *Assistant Resident Physician, Hospital of The Rockefeller Institute; Assistant, Rockefeller Institute; Lieut. (j.g.) M.C. V(S) U.S.N.R. on active duty.* (6, 1941)
- Curtis, George Morris, M.A., Ph.D., M.D. Kinsman Hall, Ohio State University, Columbus. *Professor of Surgery; Chairman, Department of Research Surgery.* (1, 1933; 4, 1933)
- Curtis, Howard J., M.A., Ph.D. 601 Florida Ave., Oak Ridge, Tenn. (1, 1940)
- Cutler, Elliott C., M.D. Peter Bent Brigham Hospital, Boston, Mass. *Moseley Professor of Surgery, Harvard Medical School; Surgeon-in-Chief, Peter Bent Brigham Hospital.* (4, 1927)
- Cutting, Reginald A., M.D., Ph.D. Georgetown University School of Medicine, 3900 Reservoir Road, N.W., Washington, D. C. *Professor of Physiology and Director of the Department.* (1, 1939)
- Cutting, Windsor C., M.D. Stanford University School of Medicine, San Francisco, Calif. *Assistant Professor of Therapeutics.* (3, 1939)
- Daft, Floyd Shelton, Ph.D. National Institute of Health, Washington, D. C. *Senior Biochemist.* (5, 1941)
- Daggs, Ray Gilbert, Ph.D. 260 N. Hanover St., Pottstown, Pa. *Lt. Col.* (1, 1935; 5, 1933)
- Dakin, Henry D., D.Sc., LL.D., Ph.D., F.I.C., F.R.S. Scarborough-on-Hudson, N. Y. (2, 1906)
- Dalton, Albert J., M.A., Ph.D. National Institute of Health, Bethesda, Md. *Cytologist.* (4, 1942)
- Dam, Henrik, D.Sc. The Rockefeller Inst. for Medical Research, 66th St. and York Ave., New York 21, N. Y. (2, 1944; 5, 1943)
- D'Amour, Fred E., M.S., Ph.D. 2311 S. Josphine St., Denver, Colo. *Associate Professor, Department of Zoology, University of Denver.* (1, 1934)
- D'Amour, Marie C., Ph.D., M.D. 2311 So. Josphine St., Denver, Colo. (1, 1934)
- Daniels, Amy L., Ph.D. College Highway, Avon, Conn. *Retired.* (2, 1919; 5, 1933)
- Danielson, Irvin S., Ph.D. Pearl River Apartments, Apt. 3H, Pearl River, N. Y. *Research Chemist.* (2, 1937)
- Dann, W. J., Ph.D., D.Sc. Duke University School of Medicine, Durham, N. C. *Associate Professor of Physiology.* (2, 1937)
- Darby, William J., M.D., Ph.D. Vanderbilt Univ. School of Medicine, Nashville, Tenn. *Assistant Professor of Biochemistry, Assistant Professor of Medicine.* (5, 1945)
- Darling, Robert Croly, M.D.\* 25 Hammond St., Cambridge, Mass. *Assistant Professor of Industrial Physiology, Harvard University.* (1, 1944)
- Darrow, Chester W., Ph.D. Institute for Juvenile Research, 907 S. Wolcott St., Chicago, Ill. *Research Psychologist, Institute for Juvenile Research; Associate in Physiology, University of Illinois College of Medicine.* (1, 1937)
- Darrow, Daniel Cady, M.D. New Haven Hospital, New Haven, Conn. *Associate Professor of Pediatrics, Yale University.* (2, 1936)
- Davenport, Horace Willard, B.S., B.Sc. (Oxon) Ph.D. Dept. of Physiology, University of Utah, Salt Lake City 1. (1, 1942)
- David, Norman Austin, M.D. University of Oregon Medical School, Portland. *Professor of Pharmacology.* (3, 1934)
- Davidsohn, Israel, M.D. Mount Sinai Hospital, 2750 W. 15th Place, Chicago, Ill. *Pathologist and Director of Laboratories, Mt. Sinai Hospital; Associate Professor of Pathology, College of Medicine, University of Illinois.* (4, 1939; 6, 1929)
- Davis, George Kelso, Ph.D. Nutrition Laboratory, Animal Industry Dept., Agricultural Experiment Station, Gainesville, Fla. *Nutritional Technologist and Biochemist, Univ. of Florida, Florida Agricultural Experiment Station.* (5, 1944)
- Davis, Hallowell, M.D. Harvard Medical School, Boston, Mass. *Associate Professor of Physiology.* (1, 1925)
- Davis, Harry A., M.D., C.M. Dept. of Surgery, School of Medicine, Louisiana State University, 1542 Tulane Avenue, New Orleans. *Associate Professor of Surgery.* (4, 1944)

- Davis, John Emerson, M.S., Ph.D. Univ. of Arkansas-School of Medicine, Little Rock. Associate Professor of Pharmacology and Physiology. (1, 1941; 3, 1941)
- Davson, Hugh, M.Sc., D.Sc. Dalhousie University, Halifax, N.S., Canada. Experimental Station, Porton, Wilts, England. Associate Professor of Physiology. (1, 1941)
- Dawson, James Robertson, Jr., M.D. Vanderbilt Medical School, Nashville, Tenn. Associate Professor. (4, 1940)
- Dawson, Percy M., M.D. Duke University Medical School, Durham, N. C. Visiting Professor, Dept. of Physiology. (1, 1900)
- Day, Harry G., D.Sc. University of Indiana, Bloomington. Associate Professor, Dept. of Chemistry. (5, 1940)
- Day, Paul L., M.A., Ph.D. University of Arkansas School of Medicine, Little Rock. Professor of Physiological Chemistry. (2, 1934; 5, 1933)
- de Beer, Edwin J., Ph.D. The Wellcome Research Laboratories, Tuckahoe, N. Y. Assistant Director of Research. (3, 1944)
- De Bodo, Richard C., M.D. 477 First Ave., New York, N. Y. Associate Professor of Pharmacology, New York Univ. College of Medicine. (1, 1932; 3, 1931)
- DeEds, Floyd, M.A., Ph.D. 344 Santa Ana Ave., San Francisco, Calif. Principal Pharmacologist, Western Regional Research Laboratory, 800 Buchanan St., Albany, Calif. (2, 1937; 3, 1927)
- Defendorf, James Holmes, Ph.D. Office of the Chief of the Chemical Warfare Service, Washington, D. C. Colonel, *Sn.C.* (3, 1940)
- de Gara, Paul F., M.D. 200 Pinehurst Ave., New York City. Instructor in Pathology, Cornell University Medical College. (6, 1941)
- DeGraff, Arthur C., M.D. New York University College of Medicine, New York City. Professor of Therapeutics. (3, 1937)
- Deichmann, Wilhelm, M.Sc., Ph.D. 527 McAlpin, Cincinnati, O. Instructor, Kettering Laboratory of Applied Physiology; Instructor in Physiology, University of Cincinnati, College of Medicine. (3, 1941)
- del Pozo, E. C., M.D.\* Medellin 196, Mexico, D. F., Mexico. (1, 1943)
- Dempsey, Edward W., Sc.M., Ph.D. Harvard Medical School, Boston, Mass. Instructor in Physiology. (1, 1940)
- Derbyshire, Arthur J., Ph.D. Wayne University College of Medicine, Detroit, Mich. Associate Professor of Physiology. (1, 1939)
- de Savitsch, Eugene, M.D. Suite 24, 1150 Connecticut Ave., Washington, D. C. Clinical Instructor in Surgery, Georgetown University School of Medicine. (4, 1934)
- Deuel, Harry J., Jr., Ph.D. University of Southern California Medical School, Los Angeles. Professor of Biochemistry. (1, 1928; 2, 1924; 5, 1933)
- Deulofeu, Venancio, D. Chem. Casilla Correo 2539, Buenos Aires, Argentina. Professor of Organic Chemistry, University of Buenos Aires. (2, 1942)
- Dey, Frederick L., Ph.D., M.D.\* 5928 N. Paulina St., Chicago, Ill. *Lt. (j.g.), USNR.* (1, 1945)
- Dienes, Loniis, M.D. Massachusetts General Hospital, Boston. Bacteriologist. (6, 1924)
- Dill, David Bruce, M.A., Ph.D. Fatigue Laby., Soldiers Field, Harvard Univ., Boston, Mass. Professor of Industrial Physiology. (1, 1941; 2, 1927; 5, 1936)
- Dille, James M., M.S., Ph.D. University of Illinois School of Medicine, 1853 Polk St., Chicago. (3, 1939)
- Dillon, Robert T., M.S., Ph.D. % G. D. Searle and Co., Box 5110, Chicago 80, Ill. Head, Analytical Division. (2, 1934)
- Dingle, John H., Sc.D., M.D. Respiratory Diseases Comm. Lab., Station Hospital, Section 2, Fort Bragg, N. C. (6, 1941)
- Di Palma, Joseph R., M.D.\* Long Island College of Medicine, 350 Henry St., Brooklyn, N. Y. Instructor in Medicine. (1, 1943)
- Dische, Zacharias, M.D. Dept. of Biochemistry, College of Physicians and Surgeons, 630 W. 168th St., New York City. (2, 1944)
- Dixon, Harold M., M.D. University of Pennsylvania, Philadelphia. Associate in Pathology; Chief of the Division of Pathology, Philadelphia General Hospital. (4, 1936)
- Doan, Charles A., M.D. Ohio State University, College of Medicine, Columbus. Dean; Professor of Medicine; Director of Medical Research. (4, 1928)
- Dochez, A. Raymond, M.D., Sc.D. (hon.). Presbyterian Hospital, 620 W. 168th St., New York City. John E. Borne Professor of Medical and Surgical Research, Columbia University; Member of National Academy of Sciences. (4, prior to 1920; 6, 1922)
- Dohan, F. Curtis, M.D. 80 Princeton Rd., Cynwyd, Pa. Fellow, George S. Cox Medical Research Institute; Associate in Medicine, University of Pennsylvania, Philadelphia. (1, 1941)
- Doisy, Edward A., M.S., Ph.D., Sc.D. St. Louis University School of Medicine, St. Louis 4, Mo. Professor of Biological Chemistry; Member, National Academy of Sciences. (2, 1920)
- Dominguez, Rafael, M.D. Saint Luke's Hospital, 11311 Shaker Blvd., Cleveland, O. Director of Laboratories, St. Luke's Hospital; Associate in Pathology, Western Reserve University. (1, 1935)
- Donahue, D. D., D.Sc. Division of Industrial Hygiene, National Institute of Health, Bethesda,

- Md. Physiologist, Toxicology Section, Division of Industrial Hygiene, U. S. Public Health Service. (3, 1941)
- Dooley, M. S., M.D. 766 Irving Ave., Syracuse, N. Y. Professor of Pharmacology, College of Medicine, Syracuse University. (3, 1923)
- Dorfman, Ralph I., Ph.D. Dept. of Biochemistry, Western Reserve University School of Medicine, Cleveland, O. Assistant Professor of Biochemistry. (2, 1940)
- Dotti, Louis Basil, M.A., Ph.D. St. Luke's Hospital, Amsterdam Ave. and 113th St., New York City. Chemist, St. Luke's Hospital; Lecturer in Physiology and Biochemistry, New York Medical College. (1, 1937)
- Doty, J. Roy, Ph.D. American Dental Association Bureau of Chemistry, 222 E. Superior St., Chicago, Ill. Associate Chemist. (2, 1941)
- Dounce, Alexander L., Ph.D. Strong Memorial Hospital, 260 Crittenden Blvd., Rochester, N. Y. Instructor in Biochemistry, University of Rochester, School of Medicine and Dentistry. (2, 1944)
- Dow, Philip, Ph.D. University of Georgia School of Medicine, Augusta. Associate Professor of Physiology. (1, 1939)
- Dow, Robert S., M.D., Ph.D. University of Oregon Medical School, Portland. Associate Professor of Anatomy. (1, 1940)
- Downs, Ardrey W., M.A., M.D., D.Sc., F.A.C.P. University of Alberta, Edmonton, Canada. Professor of Physiology and Pharmacology. (1, 1917)
- Downs, Cora M., Ph.D. 1625 Alabama St., Lawrence, Kan. (6, 1929)
- Drabkin, David L., M.D. Medical School, University of Pennsylvania, Philadelphia. Associate Professor of Physiological Chemistry. (2, 1928; 5, 1934)
- Dragstedt, Carl A., Ph.D., M.D. Northwestern University Medical School, 303 E. Chicago Ave., Chicago, Ill. Professor of Pharmacology. (1, 1928; 3, 1932)
- Dragstedt, Lester R., M.D., Ph.D. University of Chicago, Chicago, Ill. Professor of Surgery. (1, 1920)
- Draize, J. H., Ph.D. Division of Pharmacology, Food & Drug Administration, U. S. Dept. of Agriculture, Washington, D. C. Pharmacologist. (3, 1940)
- Drake, T. G. H., M.B., F.R.C.P. (e). University of Toronto, Toronto, Canada. Junior Demonstrator in Paediatrics, Department of Medicine, University of Toronto; Clinical Assistant on Active Staff and Associate Director Research Laboratory, Hospital for Sick Children. (5, 1936)
- Draper, William B., M.Sc., M.D. University of Colorado School of Medicine, 4200 E. 9th Ave., Denver. Associate Professor of Physiology and Pharmacology. (3, 1938)
- Dreisbach, Robert H., Ph.D., M.D. Stanford University School of Medicine, San Francisco 15, Calif. Instructor. On leave: Capt., MC, 0491982, Lovell General Hospital, Ft. Devens, Mass. (3, 1945)
- Dresbach, Melvin, M.S., M.D. Hahnemann Medical College, Philadelphia, Pa. Visiting Fellow in Physiology. (1, 1912)
- Dreyer, Nicholas Bernard, M.A. (Oxon) School of Medicine, University of Vermont, Burlington. Associate Professor of Physiology and Pharmacology. (3, 1942)
- Drill, Victor Alexander,\* Ph.D. Dept. of Pharmacology, Yale University School of Medicine, 333 Cedar St., New Haven, Conn. Instructor in Pharmacology. (1, 1943)
- Drinker, Cecil K., M.D. Harvard University School of Public Health, Boston, Mass. Professor of Physiology and Dean. (1, 1915)
- Drinker, Katherine R., M.D. Harvard School of Public Health, 55 Shattuck St., Boston, Mass. Instructor in Public Health. (1, 1915)
- Dripps, Robert D., M.D. School of Medicine, University of Pennsylvania, Philadelphia 4. Assistant Professor of Anesthesiology, Associate in Pharmacology. (3, 1945)
- Driver, Robert L., Ph.D.\* University of Alabama, School of Medicine, Box 1503, University. Instructor in Physiological Chemistry and Physiology. (1, 1945)
- Drury, Douglas R., M.D. University of Southern California, Los Angeles. Professor of Physiology. (1, 1932)
- Dubin, Harry E., Ph.D. 250 E. 43rd St., New York City. President, H. E. Dubin Laboratories, Inc. (2, 1925)
- DuBois, Eugene F., M.D. Cornell University Medical School, 1300 York Ave., New York, N. Y. Professor and Head of the Department of Physiology and Biophysics; Attending Physician, New York Hospital; Member, National Academy of Sciences; Captain (M.C.) U.S.N.R. (1, 1913; 3, 1921; 5, 1935)
- Dubos, René J., Ph.D., D.Sc. Rockefeller Institute for Medical Research, 66th St. and York Ave., New York City. Member. (6, 1938)
- Dukes, H. H., D.V.M., M.S. New York State Veterinary College, Cornell University, Ithaca, N. Y. Professor of Veterinary Physiology. (1, 1934)
- Dulaney, Anna D., A.M., Ph.D. Pathological Institute, University of Tennessee, Memphis. Assistant Professor of Bacteriology, Medical School. (6, 1924)
- Dumke, Paul Rudolph, M.D. Clinical Research Section, Medical Research Lab., Edgewood Arsenal, Edgewood, Md. Instructor in Pharma-

- cology, University of Pennsylvania; Captain, M.C. (3, 1942)
- Dunlap, Charles E., M.D. Tulane University of Louisiana, 1430 Tulane Ave. New Orleans. Associate Professor of Pathology. (4, 1942)
- Dunn, Max Shaw, Ph.D. University of California, Los Angeles. Professor of Chemistry. (2, 1933)
- Dunn, Thelma Brumfield, M.D. The National Cancer Institute, Bethesda, Md. Research Fellow. (4, 1945)
- Durrant, Edwin Poe, M.A., Ph.D. Ohio State University, Columbus. Associate Professor of Physiology. (1, 1928)
- Dutcher, R. Adams, M.S., M.A., D.Sc. Pennsylvania State College, State College. Professor and Head of Department of Agricultural Biochemistry. (2, 1920; 5, 1933)
- Duval, Charles Warren, M.D. San José Hospital, San José, Calif. (4, 1913)
- du Vigneaud, Vincent, M.S., Ph.D. Cornell University Medical College, 1300 York Ave., New York 21, N. Y. Professor of Biochemistry; Member, National Academy of Sciences. (2, 1929; 5, 1934)
- Dworkin, Simon, D.D.S., M.D., C.M. Biology Building, McGill University, Montreal, Quebec, Canada. Lecturer in Physiology, Faculty of Medicine. (1, 1931)
- Dye, J. A., Ph.D. James Law Hall, Cornell University, Ithaca, N. Y. Associate Professor of Physiology. (1, 1929)
- Dye, Marie, M.S., Ph.D. Michigan State College, East Lansing. Dean of Division of Home Economics. (2, 1929; 5, 1933)
- Dyer, Helen M., M.S., Ph.D. National Cancer Institute, U.S.P.H.S., Bethesda, Md. Research Fellow. (2, 1936; 5, 1937)
- Eadie, George S., Ph.D. Duke University School of Medicine, Box 3709, Durham, N. C. Professor of Physiology and Pharmacology. (1, 1929; 3, 1940)
- Eagle, Harry, M.D. Johns Hopkins Hospital, Baltimore, Md. Senior Surgeon, U. S. Public Health Service; Lecturer in Venereal Diseases, Johns Hopkins University Medical School. (4, 1936)
- Earle, Wilton R., Ph.D. U. S. Public Health Service, National Cancer Institute, Bethesda, Md. Principal Cytologist. (4, 1940)
- Eaton, Alonzo Guy, M.A., Ph.D. Louisiana State University Medical Center, New Orleans. Associate Professor of Physiology. (1, 1933)
- Eaton, Monroe D., M.D. State Department of Public Health, Influenza Laboratory, 1392 University Ave., Berkeley, Calif. Staff Member, International Health Division of The Rockefeller Foundation. (6, 1937)
- Ecker, E. E., Ph.D. School of Medicine, Western Reservo University, 2085 Adelbert Rd., Cleveland, O. Professor of Immunology. (4, 1925)
- Eckstein, Henry C., M.S., Ph.D. 320 W. Medical Building, University of Michigan, Ann Arbor. Associate Professor of Biological Chemistry. (2, 1925)
- Eddy, Nathan B., M.D. National Institute of Health, Bethesda, Md. Principal Pharmacologist, United States Public Health Service. (1, 1919; 3, 1929)
- Eddy, Walter H., A.M., Ph.D. 60 E. 42nd St., New York, N. Y. Professor Emeritus, Physiological Chemistry, Teachers College, Columbia University. (2, 1913; 5, 1933)
- Edsall, Geoffrey, M.D. Antitoxin and Vaccine Laboratory, 375 South St., Jamaica Plain, Mass. Acting Director, Division of Biologic Laboratories, Massachusetts Department of Public Health; Associate in Public Health Laboratory Methods, Simmons College; Instructor in Applied Immunology, Harvard School of Public Health. (6, 1943)
- Edsall, John Tileston, M.D. Harvard Medical School, Boston, Mass. Associate Professor of Biological Chemistry and Tutor in Biochemical Sciences. (2, 1931)
- Edwards, Dayton J., Ph.D. 1300 York Ave., New York City. Associate Professor of Physiology; Assistant Dean, Cornell University Medical College. (1, 1921)
- Edwards, Jesse E., M.D. 25 Edgehill Rd., Brookline, Mass. (4, 1941)
- Edwards, J. Graham, A.M., Ph.D. 24 High St., Buffalo, N. Y. Assistant Professor of Anatomy, University of Buffalo. (1, 1932)
- Eggerth, Arnold H., Ph.D. Hoagland Laboratory, 335 Henry St., Brooklyn, N. Y. Associate Professor of Bacteriology, Long Island College of Medicine. (4, 1925)
- Ehrenstein, Maximilian R., Ph.D. 806 Maloney Clinic, University of Pennsylvania Hospital, 36th and Spruce Sts., Philadelphia. Assistant Professor of Chemistry assigned to Medicine. (2, 1942)
- Ehrlich, William E., M.D. University of Pennsylvania Medical School, Philadelphia. Assistant Professor of Pathology. (4, 1945)
- Eichelberger, Lillian, Ph.D. University of Chicago, Dept. of Medicine, Chicago, Ill. Associate Professor of Biochemistry. (2, 1937)
- Eiseman, Anna J., Ph.D. U. S. Public Health Service Hospital, Lexington, Ky. Biological Chemist. (2, 1930)
- Elderfield, Robert C., Ph.D. Columbia University, New York City. Professor of Chemistry. (2, 1934)
- Elftman, Herbert, M.A., Ph.D. College of Physicians and Surgeons, Columbia University, 630

- W. 168th St., New York City. *Assistant Professor in Anatomy.* (1, 1940)
- Eliot, Martha M., M.D.** United States Children's Bureau, Washington, D. C. *Assistant Chief.* (5, 1933)
- Elliott, K. Allan C., M.Sc., Ph.D.** Montreal Neurological Institute, 3801 University St., Montreal, Canada. *Assistant Professor in Neurology, McGill University.* (2, 1937)
- Ellis, Frederick W., M.D.** Monson, Mass. (1, 1887)
- Ellis, Fred W., M.S., Ph.D.** University of North Carolina, Chapel Hill. *Assistant Professor of Pharmacology.* (3, 1945)
- Ellis, Lillian N., Ph.D.** Adelphi College, Garden City, N. Y. (5, 1940)
- Ellis, Max Mapes, A.M., Ph.D., Sc.D.** Medical School, University of Missouri, Columbia. *Professor of Physiology and Pharmacology.* (1, 1923)
- Ellis, N. R., M.S.** Bureau of Animal Industry, U. S. Department of Agriculture, Agricultural Research Center, Beltsville, Md. *Principal Chemist, Animal Husbandry Division.* (2, 1928; 5, 1933)
- Elser, William J., M.D.** Kent, Conn. (6, 1920)
- Elvehjem, Conrad Arnold, M.S., Ph.D., Sc.D.** Biochemistry Building, University of Wisconsin, Madison. *Professor of Biochemistry; Member, National Academy of Sciences.* (2, 1931; 5, 1933)
- Emerson, George A., M.S., Ph.D.** University of Texas, Medical Branch, Galveston. *Professor of Pharmacology.* (3, 1935)
- Emerson, Gladys A., Ph.D.** Merck Institute of Therapeutic Research, Rahway, N. J. *Nutritionist.* (5, 1942)
- Emerson, Oliver H., Ph.D.** Western Regional Research Laboratory, U. S. Dept. of Agriculture, Albany 6, Calif. *Associate Chemist.* (2, 1938)
- Emery, Frederick E., D.V.M., M.S., Ph.D.** University of Arkansas School of Medicine, Little Rock. *Professor of Physiology and Pharmacology.* (1, 1930)
- Emmett, Arthur D., M.A., Ph.D.** Research Department, Parke, Davis & Co., Detroit, Mich. *Assistant Director of Research.* (2, 1908; 5, 1933)
- Enders, John F., A.M., Ph.D.** Department of Bacteriology, Medical School, Harvard University, Boston, Mass. *Assistant Professor of Bacteriology and Immunology.* (6, 1936)
- Engle, Earl Theron, Ph.D.** College of Physicians and Surgeons, Columbia University, 630 W. 168th St., New York City. *Professor of Anatomy.* (1, 1930)
- Epstein, Albert A., M.D.** 1111 Madison Ave., New York City. *Physician, Beth Israel Hos-*
- pital; Physician, Hospital for Joint Diseases.* (2, 1912)
- Erickson, Cyrus C., M.D.** Duke University School of Medicine, Durham, N. C. *Associate in Pathology.* (4, 1941)
- Erlanger, Joseph, M.D., LL.D., Sc.D.** Washington University School of Medicine, 4580 Scott Ave., St. Louis, Mo. *Professor of Physiology; Member of the National Academy of Sciences.* (1, 1901)
- Espe, Dwight L., Ph.D.** Iowa State College, Ames. *Assistant Research Professor in Dairy Husbandry.* (1, 1940)
- Essex, Hiram E., M.S., Ph.D.** Mayo Foundation, Rochester, Minn. *Professor of Physiology, Institute of Experimental Medicine.* (1, 1932; 3, 1940)
- Ettinger, C. H., M.D., C.M., F.R.S.C.\*** Queen's University, Kingston, Canada. *Professor of Physiology.* (1, 1943)
- Evans, Earl Alison, Jr., Ph.D.** Department of Biochemistry, University of Chicago, Chicago, Ill. *Professor and Chairman of Department.* (2, 1939)
- Evans, Everett Idris, M.D., Ph.D.** Department of Surgery, Medical College of Virginia, Richmond. *Assistant Professor of Surgery.* (1, 1935)
- Evans, Gerald Taylor, M.D., Ph.D.** University of Minnesota Hospitals, Minneapolis. *Director of Laboratory Service, University of Minnesota Hospitals; Associate Professor of Medicine, University of Minnesota.* (1, 1942)
- Evans, Herbert M., M.D.** University of California, Berkeley. *Professor of Anatomy and Director of Institute of Experimental Biology; Member of the National Academy of Sciences.* (1, 1919)
- Evans, William E., Jr., M.S., Ph.D.** University of Maryland Medical School, Baltimore. *Assistant Professor of Pharmacology.* (3, 1940)
- Eveleth, D. F., Ph.D., D.V.M.** North Dakota Agricultural College, Fargo. *Professor, Veterinary Science, North Dakota Agricultural Experiment Station.* (2, 1939)
- Everett, Mark Reuben, Ph.D.** University of Oklahoma Medical School, Oklahoma City. *Professor of Biochemistry.* (2, 1929)
- Ewing, P. L., M.S., Ph.D.** University of Texas School of Medicine, Galveston. *Associate Professor of Pharmacology.* (3, 1938)
- Eyster, John A. English, M.D.** University of Wisconsin, Madison. *Professor of Physiology.* (1, 1906; 3, 1908)
- Fahr, George, M.D.** 102 Millard Hall, University of Minnesota Medical School, Minneapolis. *Professor of Clinical Medicine.* (1, 1913; 3, 1940)

- Failey, Crawford F., Ph.D. 947 East 58th St., Chicago 37, Ill. Associate Professor of Biochemistry, University of Chicago. (2, 1933)
- Fairhall, Lawrence T., M.A., Ph.D. U. S. Public Health Service, Washington, D. C. Principal Industrial Toxicologist. (2, 1924)
- Falk, Carolyn R., B.A. 40 E. 66th St., New York City. Bacteriologist, Bureau of Laboratories, New York City Dept. of Health. (6, 1943)
- Falk, K. George, Ph.D. 40 E. 66th St., New York City. Director, Laboratory of Industrial Hygiene. (2, 1913)
- Famulener, Lemuel W., Ph.C., M.D. 275 Engle St., Englewood, N. J. (6, 1920)
- Farber, Sidney, M.D. Harvard Medical School, 25 Shattuck St., Boston, Mass. Assistant Professor of Pathology. (4, 1934)
- Farmer, Chester J., A.M. Northwestern Medical School, 303 E. Chicago Ave., Chicago, Ill. Professor of Chemistry. (2, 1935)
- Farr, Lee E., M.D. Alfred I. duPont Institute, Wilmington, Del. Director of Research. (4, 1941)
- Farrell, James I., Ph.D., M.D. 17 Chataqua Pl., Bradford, Pa. (1, 1938)
- Fassett, David W., M.D. Department of Therapeutics, New York University College of Medicine, 414 E. 26 St., New York City. Fellow, Department of Therapeutics. (3, 1942)
- Favorite, Grant O., M.D. 1313 Andover Rd., Overbrook, Philadelphia, Pa. Professor of Bacteriology, Hahnemann Medical College, Philadelphia. (6, 1943)
- Fay, Marion, M.A., Ph.D. Woman's Medical College of Pennsylvania, East Falls, Philadelphia 29. Professor of Physiological Chemistry. (2, 1937)
- Feldman, Harry A., M.D. University of Tennessee, Memphis. Fellow (on leave) in Medicine, Harvard Medical School; Capt., AUS, Chief Div. Bact. (6, 1943)
- Feldman, William H., D.V.M., M.S. The Mayo Foundation, Rochester, Minn. Associate in the Division of Experimental Surgery and Pathology. (4, 1934)
- Fell, Norbert, Ph.D. Parke, Davis & Co., Detroit, Mich. In charge of Immunochemical Research. (6, 1944)
- Feller, Alto E., M.D. Commission on Acute Respiratory Diseases, Station Hospital, Section 2, Fort Bragg, N. C. Consultant to Secretary of War. (6, 1943)
- Fellows, Edwin J., M.S., Ph.D. Temple University School of Medicine, Philadelphia, Pa. Assistant Professor of Pharmacology. (3, 1939)
- Felton, Lloyd D., M.D., D.Sc. Division of Infectious Diseases, National Institute of Health, 25th and E Sts., N.W., Washington, D. C. Senior Surgeon, United States Public Health Service. (6, 1926)
- Fenn, Wallace Osgood, A.M., Ph.D. University of Rochester School of Medicine and Dentistry, 260 Crittenden Blvd., Rochester, N. Y. Professor of Physiology; Member, National Academy of Sciences. (1, 1924)
- Fenning, Con, M.D., M.A. University of Utah School of Medicine, Salt Lake City. Professor of Pharmacology and Physiology. (1, 1942)
- Ferguson, James Kenneth Wallace, M.A., M.D. 76 Kilbarry Rd., Toronto, Ontario, Canada. Assistant Professor of Pharmacology, University of Toronto. Wing Commander, R.C.A.F. (1, 1933; 3, 1941)
- Ferguson, John Howard, M.D., M.A., L.M.S.S.A. Dept. of Physiology, School of Medicine, University of North Carolina, Chapel Hill. Professor of Physiology and Acting Professor of Pharmacology. (1, 1933; 3, 1939)
- Ferguson, L. Kraer, M.D. 133 S. 36th St. Philadelphia, Pa. Assistant Professor of Surgery, University of Pennsylvania; Surgeon, Philadelphia General Hospital; Assistant Surgeon, University of Pennsylvania Hospital. (4, 1935)
- Ferry, John Douglass, Ph.D. Department of Physical Chemistry Harvard Medical School, 25 Shattuck St., Boston, Mass. Research Associate. (2, 1941)
- Ferry, Newell S., M.D., Parke, & Davis Co Detroit, Mich. Assistant Director of Research. (6, 1916)
- Ferry, Ronald M., M.D. 966 Memorial Drive, Cambridge, Mass. Master of John Winthrop House. (2, 1924)
- Fletcher, Edwin S., Jr., Ph.D.\* 1800 Shroyer Road, Dayton, Ohio. Special Consultant to the Army Air Forces, AAF Materiel Command, Wright Field. (1, 1944)
- Fetter, Dorothy, Ph.D.\* Department of Hygiene, Brooklyn College, Brooklyn, N. Y. Instructor in Physiology. (1, 1944)
- Fevold, Harry L., M.S., Ph.D. Western Regional Research Laboratory, Albany 6, Calif. Biochemist, U. S. Dept. of Agriculture. (2, 1942)
- Field, John, II, A.M., Ph.D. Stanford University, Stanford, Calif. Professor of Physiology. (1, 1930)
- Fincke, Margaret L., Ph.D. Oregon State College, Corvallis. Associate Professor of Foods and Nutrition, School of Home Economics. (5, 1940)
- Findley, Thomas, Jr., M.D. Ochsner Clinic, 3503 Prytania, New Orleans, La. Head of the Department of Internal Medicine, Ochsner Clinic, New Orleans; Assistant Professor of Clinical Medicine, Tulane University School of Medicine. (1, 1938)

- Fine, Morris S., Ph.D. Central Laboratories, General Foods Corporation, Hoboken, N. J. Director of Research. (2, 1912; 5, 1933)
- Finland, Maxwell, B.S. Boston City Hospital, Boston, Mass. Assistant Professor of Medicine, Harvard Medical School. (6, 1941)
- Firor, Warfield Monroe, M.D. Johns Hopkins Hospital, Baltimore, Md. Associate Professor of Surgery, Johns Hopkins University. (1, 1932)
- Fischer, Ernst, M.D., Dr. habil. Medical College of Virginia, Richmond. Professor of Physiology (1, 1936)
- Fischer, Hermann O. L., Ph.D. Banting Institute, 100 College St., University of Toronto, Toronto 5, Canada. Research Professor of Organic Chemistry. (2, 1940)
- Fischer, Martin H., M.D., Pharm. D. (hon.), Sc.D. University of Cincinnati College of Medicine, Eden Ave., Cincinnati 19, O. Professor of Physiology. (1, 1901; 2, 1919)
- Fishberg, Ella H., M.A., M.D. Beth Israel Hospital, Stuyvesant Park East, New York City. Biochemist. (2, 1931)
- Fisher, Albert Madden, M.A., Ph.D. Connaught Laboratories, University of Toronto, Toronto, Canada. Research Associate. (2, 1944)
- Fisher, Kenneth C., M.A., Ph.D. University of Toronto, Toronto, Ont., Canada. Assistant Professor of Physiological Zoology. (1, 1940)
- Fiske, Cyrus H., M.D. Harvard Medical School, Boston, Mass. Professor of Biological Chemistry. (2, 1914)
- Fitzgerald, Mabel P., 54 A, George Sq., Edinburgh, Scotland. (1, 1913)
- Fitzhugh, O. Garth, Ph.D. Division of Pharmacology, Food and Drug Administration, Federal Security Agency, Washington, D. C. Pharmacologist. (3, 1940)
- Fleischmann, Walter, M.D., Ph.D. Harriet Lane Home, Johns Hopkins Hospital, Baltimore, Md. Associate in Pediatrics, Johns Hopkins University. (1, 1940)
- Fleisher, Moyer S., M.D. Jewish Hospital, St. Louis, Mo. Research Bacteriologist. (4, 1924; 6, 1932)
- Flexner, Louis B., M.D. Department of Embryology, Carnegie Institution of Washington, Wolfe and Madison Sts., Baltimore, Md. Research Associate. (1, 1933)
- Flock, Eunice V., Ph.D. Mayo Clinic, Rochester, Minn. Assistant Professor of Biochemistry, University of Minnesota; Associate Professor in Experimental Medicine, The Mayo Foundation. (2, 1940)
- Florman, Alfred L., M.D. 708 Newark Ave., Jersey City, N.J. (6, 1942)
- Flosdorff, Earl W., Ph.D. Forest Grove, Bucks Co., Pa. Research—University of Pennsylvania School of Medicine. (6, 1941)
- Floyd, Cleveland, M.D., Sc.D. 246 Marlborough St., Boston, Mass. Chief Examiner, Boston Health Dept. (6, 1916)
- Foa, Piero Pio, Ph.D.\* 710 S. Wolcott St., Chicago, Ill. Assistant Professor of Physiology, Chicago Medical School. (1, 1944)
- Folch, Jordi, M.D. McLean Hospital, Waverly, Mass. Assistant Professor of Biological Chemistry, Harvard Medical School. Director of Scientific Research, McLean Hospital. (2, 1941)
- Follensby, Edna M., Ph.G. 80 E. Concord St., Boston, Mass. Research Assistant, Evans Memorial. (6, 1933)
- Follis, Richard H., Jr., M.D. Duke Univ. Medical School, Durham, N. C. Associate Professor of Pathology. (4, 1942)
- Foot, Nathan Chandler, M.D. 340 E. 72nd St., New York City. Professor of Surgical Pathology, Cornell University Medical College; Surgical Pathologist, New York Hospital. (4, 1924)
- Forbes, Alexander, A. M., M.D. Harvard Medical School, Boston, Mass. Professor of Physiology; Member of the National Academy of Sciences. (1, 1910)
- Forbes, Ernest B., Ph.D. State College, Pa. Director of the Institute of Animal Nutrition. (1, 1917; 5, 1935)
- Forbes, Henry S., M.D. Forest St., Milton, Mass. Associate in Neuropathology, Harvard Medical School. (1, 1931)
- Forbes, John C., M.A., Ph.D. Medical College of Virginia, Richmond. Research Professor of Biochemistry. (2, 1937)
- Forbes, William H., M.A., Ph.D.\* Harvard University, Fatigue Laboratory, Boston, Mass. Research Fellow, Assistant Director of Fatigue Lab., Assistant Professor of Industrial Physiology. (1, 1943)
- Fosdick, Leonard S., Ph.D. 311 E. Chicago Ave., Chicago, Ill. Professor of Chemistry, Northwestern University. (2, 1944)
- Foster, G. L., Ph.D. College of Physicians and Surgeons, 630 W. 168th St., New York City. Associate Professor of Biological Chemistry. (2, 1923)
- Foster, Harry E., M.D. Cutter Laboratory, Berkeley, Calif. Medical Director. (6, 1913)
- Foster, Robert H. K., Ph.D., M.D. St. Louis University School of Medicine, St. Louis, Mo. Associate Professor of Pharmacology. (1, 1940; 3, 1944)
- Foster, Ruth A. C., Ph.D. Dept. of Botany and Bacteriology, University of Texas, Austin. Instructor. (6, 1943)
- Fothergill, LeRoy D., M.D. Harvard Medical School, Boston 15, Mass. Assistant Professor of Bacteriology and Immunology. (6, 1936)

- Fraenkel-Conrat, Heinz, M.D., Ph.D. Western Regional Research Laboratory, U. S. Dept. of Agriculture, Albany 6, Calif. *Chemist.* (2, 1942)
- Francis, Thomas, Jr., M.D., M.S. (hon.), Sc.D. (hon.). School of Public Health, University of Michigan, Ann Arbor. *Professor of Epidemiology.* (4, 1940; 6, 1930)
- Franke, Florent E., M.D. 9 Sylvester, Webster Groves, Mo. *Assistant Professor of Physiology, St. Louis University School of Medicine.* (1, 1934)
- Frankel, Edward M., Ph.D. 214 River Rd., Nyack, N. Y. *Consulting Chemist.* (2, 1916)
- Fraser, Alexander MacLeod, A.M., M.D., C.M. McGill University, Montreal, Canada. *Lecturer in Pharmacology.* (3, 1939)
- Fraser, Donald T., M.B. Connaught Laboratories, University of Toronto, Toronto 5, Canada. *Professor of Hygiene and Preventive Medicine.* (6, 1935)
- Free, Alfred H. School of Medicine, Western Reserve University, Cleveland, O. *Asst. Professor of Biochemistry.* (5, 1944)
- Freeman, Harry, M.D. Worcester State Hospital, Worcester, Mass. *Internist, Research Service.* (1, 1939)
- Freeman, Leslie Willard, Ph.D., M.D.\* 2111—15th Street A, Moline, Ill. *Lt., Medical Corps, AUS.* (1, 1944)
- Freeman, Norman, E., M.D. University of Pennsylvania Medical School, Philadelphia. *J. Wm. White, Assistant Professor of Research Surgery.* (1, 1936)
- Freeman, Smith, M.D., Ph.D. Northwestern University School of Medicine, 303 E. Chicago Ave., Chicago, Ill. *Assistant Professor of Physiology and Pharmacology.* (1, 1937)
- Freund, Jules, M.D. Public Health Research Institute of the City of New York, Foot of E. 15th St., New York, N. Y. *Member.* (4, 1930; 6, 1924)
- Friedemann, Theodore E., M.A., Ph.D. Northwestern University Medical School, 303 E. Chicago Ave., Chicago, Ill. *Associate Professor of Physiology.* (2, 1925)
- Friedemann, Ulrich, M.D. Department of Bacteriology, The Jewish Hospital of Brooklyn, Classon and St. Marks Ave., Brooklyn, N. Y. (6, 1938)
- Friedewald, William F., M.D. Emory University School of Medicine, Atlanta, Ga. *Professor of Bacteriology; Associate Professor of Medicine.* (4, 1941)
- Friedgood, Harry B., M.D. 2943 Queensburg Road, Los Angeles 34, Calif. (1, 1936)
- Friedman, Maurice H., Ph.D., M.D. Hunter Field Regional Hospital, Hunter Field, Ga. *Captain (MC) AUS, Chief, Gastro-enterology.* (1, 1929)
- Friedman, M. H. F., M.A., Ph.D. Jefferson Medical College of Philadelphia, 1025 Walnut St., Philadelphia, Pa. *Assistant Professor of Physiology.* (1, 1941)
- Friedman, Nathan B., M.D. Stanford University School of Medicine, San Francisco, Calif. *Instructor in Pathology.* Army Medical Museum, 7th & Independence, Washington, D. C. (4, 1942)
- Frisch, Arthur W., Ph.D., M.D. College of Medicine, Wayne University, Detroit, Mich. *Instructor.* (6, 1938)
- Fruton, J. S., Ph.D. Yale School of Medicine, 333 Cedar St., New Haven, Conn. *Associate Professor of Physiological Chemistry.* (2, 1938)
- Fugo, Nicholas W., M.S., Ph.D. State University of Iowa, Medical School, Iowa City. *Instructor in Pharmacology, on leave.* (3, 1944)
- Fulton, John Farquhar, M.A., Ph.D., M.D. Yale University School of Medicine, New Haven, Conn. *Sterling Professor of Physiology.* (1, 1925)
- Funk, Casimir, D.Sc., Ph.D. 186 Riverside Drive, New York 24, N. Y. (2, 1921)
- Furth, Jacob, M.D. Cornell University Medical College, 1300 York Ave., New York City. *Professor of Pathology.* (4, 1932; 6, 1930)
- Gaebler, Oliver H., Ph.D., M.D. Henry Ford Hospital, Detroit, Mich. *Associate in Chemistry.* (2, 1927)
- Gaffron, Hans, Ph.D. Chemical Department, University of Chicago, Chicago, Ill. *Research Associate (Assistant Professor).* (2, 1941)
- Gagge, Adolf Pharo, Ph.D. Aeromedical Research Laboratory, Wright Field, Dayton, O. *Lt. Col.; Chief, Biophysics Branch, Air Corps, U. S. Army; on leave from Yale University and John B. Pierce Laboratory of Hygiene.* (1, 1939)
- Galambos, Robert, M.A., Ph.D. University of Rochester School of Medicine and Dentistry, 260 Crittenden Blvd., Rochester, N. Y. (1, 1942)
- Gall, Edward A., M.D. Bethesda Hospital, Cincinnati, O. *Assistant Professor of Pathology, College of Medicine, University of Cincinnati.* (4, 1941)
- Gallagher, Thomas F., Ph.D. University of Chicago, Chicago, Ill. *Associate Professor of Biochemistry.* (2, 1932)
- Gallup, Willis D., M.S., Ph.D. Oklahoma Agricultural and Mechanical College, Stillwater. *Chemist and Professor of Agricultural Chemistry.* (2, 1932)
- Gamble, James L., M.D., S.M. 33 Edgehill Rd., Brookline, Mass. *Professor of Pediatrics, Harvard Medical School.* (2, 1922; 5, 1933)
- Gantt, W. Horsley, M.D. Phipps Psychiatric Clinic, Johns Hopkins Hospital, Baltimore, Md. *Associate in Psychiatry.* (1, 1935)
- Garbat, Abraham L., M.D. 103 E. 78th St., New York City. *Attending Physician, Lenox Hill Hospital.* (6, 1913)

- Gardner, Leroy U., M.D. Saranac Laboratory for Study of Tuberculosis, Saranac Lake, N. Y. Director of the Trudeau Foundation. (4, 1927)
- Garrey, Walter Eugene, Ph.D., M.D. Vanderbilt University School of Medicine, Nashville, Tenn. Professor Emeritus of Physiology. (1, 1910; 2, 1906)
- Gasser, Herbert S., A.M., M.D., Sc.D. (hon.) Rockefeller Institute for Medical Research, 66th St. and York Ave., New York City. Director of Laboratories; Member of the National Academy of Sciences. (1, 1915; 3, 1924)
- Gates, Olive, M.D. 25 Shattuck St., Boston, Mass. Associate Pathologist. (4, 1940)
- Gaunt, Robert, Ph.D. Washington Square College, New York University, New York City. Associate Professor of Biology. (1, 1939)
- Gay, Leslie N., M.D. 1114 St. Paul St., Baltimore, Md. Director of the Allergy Clinic, Johns Hopkins Hospital; Visiting Physician to Johns Hopkins Hospital; Associate in Medicine, Johns Hopkins University. (6, 1927)
- Geiling, E. M. K., M.S., M.D., Ph.D. University of Chicago, Chicago, Ill. Frank P. Hixon Distinguished Service Professor of Pharmacology and Chairman of Department. (1, 1933; 2, 1927; 3, 1925)
- Gelfan, Samuel, Ph.D. College of Physicians and Surgeons, Columbia University, 630 West 168th St., New York 32, N. Y. Assistant Professor of Physiology. (1, 1930)
- Gellhorn, Ernst, M.D., Ph.D. Room 116, Medical Sciences, University of Minnesota, Minneapolis. Professor of Neurophysiology. (1, 1930)
- Gemmill, Chalmers L., M.D. Medical School, University of Virginia, Charlottesville. Professor of Pharmacology. (1, 1928; 2, 1935)
- Gerard, R. W., Ph.D., M.D. University of Chicago, Chicago, Ill. Professor of Physiology. (1, 1927)
- Gerstenberger, Henry John, M.D. Western Reserve University, Cleveland, O. Professor of Pediatrics, School of Medicine, Western Reserve University; Director of Pediatrics, Babies and Children's Hospital. (5, 1938)
- Gesell, Robert, M.D. University of Michigan, Ann Arbor. Professor of Physiology. (1, 1913)
- Gettler, Alexander O., A.M., Ph.D., LL.D. New York University, 29 Washington Place, New York City. Professor of Chemistry and Toxicology; Toxicologist to Chief Medical Examiner's Office. (2, 1916)
- Gey, George Otto, M.D. Division for Cellular Pathology, Room 531, Dispensary Building, Johns Hopkins Hospital and University, Baltimore 5, Md. Instructor in Surgery. (1, 1940)
- Gibbs, Frederick Andrews, M.D. 720 N. Michigan Ave., Suite 610, Chicago, Ill. (1, 1935)
- Gibbs, Owen Stanley, M.B., Ch.B. (Edin.), M.D. 1544-46 Netherwood, Memphis 6, Tenn. Research Consultant. (1, 1935; 3, 1930)
- Gibson, Robert Banks, Ph.D. University Hospital, Iowa City, Iowa. Associate Professor of Biochemistry, State University of Iowa. (1, 1907; 2, 1906)
- Gies, William John, M.S., Ph.D., Sc.D., LL.D., F.A.C.D. 632 W. 168th St., New York City. Professor of Biological Chemistry, Columbia University. (1, 1898; 2, 1906; 3, 1909)
- Gilbert, Ruth, A.M., M.D. R.F.D. 2, Altamont, N. Y. Bacteriologist, New York State Department of Health, Albany. (6, 1920)
- Gilman, Alfred, Ph.D. Edgewood Arsenal, Md. Major, S.A.C., A.U.S. (1, 1935; 3, 1934)
- Gilson, Arthur S., Jr., A.M., Ph.D. Washington University Medical School, St. Louis, Mo. Associate Professor of Physiology. (1, 1927)
- Githens, Thomas Stotesbury, M.D. The Cambridge, Wissahickon and Chelten Aves., Germantown, Philadelphia, Pa. (1, 1915)
- Givens, Maurice H., Ph.D. Box 3836, Peninsula Station, Daytona Beach, Fla. (1, 1917; 2, 1915)
- Glaser, O. C., Ph.D. Amherst College, Amherst, Mass. Professor of Biology. (1, 1913)
- Glazko, Anthony J., Ph.D. 1732 Marin Ave., Berkeley 6, Calif. (1, 1942)
- Glick, David, Ph.D. Russell-Miller Milling Co. Minneapolis, Minn. Head, Vitamin and Enzyme Research. (2, 1936)
- Goebel, Walther F., Ph.D. The Rockefeller Institute for Medical Research, 66th St. and York Ave., New York City. Member. (2, 1929; 6, 1937)
- Goerner, Alfred, Ph.G., Pharm. D., M.D. Long Island College of Medicine, 350 Henry St., Brooklyn, N. Y. Associate Professor of Biological Chemistry. (2, 1939)
- Goetsch, Marianne, Ph.D. School of Tropical Medicine of Columbia University, San Juan, Puerto Rico. Assistant Professor of Chemistry. (2, 1933; 5, 1941)
- Gold, Harry, M.D. 1300 York Ave., New York City. Assistant Professor of Pharmacology, Cornell Medical College. (3, 1927)
- Goldblatt, Harry, M.D. Western Reserve University, Cleveland, O. Professor of Experimental Pathology, and Associate Director, Institute of Pathology. (1, 1945; 4, 1927)
- Goldfarb, Walter, M.D. 120 Station Hospital, A. P. O. 508, New York, N. Y. Captain, M.C. (1, 1938)
- Goldfarb, A. J., Ph.D. College of the City of New York, New York City. Professor of Biology. (1, 1930)
- Goldie, Horace, M.D., D.T.M. Nanuet, N. Y. City of New York, Dept. of Health. (6, 1943)

- Goldring, William, M.D. New York University College of Medicine, 477 First Ave., New York City. *Professor of Medicine.* (1, 1939)
- Goldschmidt, Samuel, Ph.D. University of Pennsylvania Medical School, Philadelphia. *Associate Professor of Physiology.* (1, 1919; 2, 1915)
- Goldsmith, Grace A. Tulane University of Louisiana, New Orleans. (5, 1943)
- Golub, Orville J., M.S. United States Naval Reserve Laboratory Research Unit No. 1, University of California, Berkeley. *Bacteriologist.* (6, 1944)
- Goodman, Louis Sanford, M.A., M.D. University of Utah School of Medicine, Salt Lake City. *Professor of Pharmacology and Chairman of the Department of Pharmacology and Physiology.* (3, 1937)
- Goodner, Kenneth, Ph.D. Rockefeller Foundation, 49 W. 49th St., New York City. *Associate.* (6, 1932)
- Goodpasture, Ernest William, M.D. Vanderbilt University Medical School, Nashville, Tenn. *Professor of Pathology and Dean.* (4, 1923)
- Gordon, Albert S., M.S., Ph.D. Washington Square College of Arts and Sciences, New York University, New York City. *Assistant Professor of Biology.* (1, 1942)
- Gordon, Harry H., M.D. 525 E. 68th St., New York City. *Associate in Pediatrics, Cornell University Medical School; Associate Attending Pediatrician, New York Hospital; Medical Officer, U. S. Dept. Labor.* (5, 1940)
- Gordon, Irving, M.D. Commission on Acute Respiratory Diseases, Station Hospital #2, Fort Bragg, N.C. (6, 1943)
- Gordon, William G., M.A., Ph.D. Eastern Regional Research Laboratory, U. S. Department of Agriculture, Chestnut Hill Station, Philadelphia, Pa. *Chemist.* (2, 1939)
- Goss, Harold, Ph.D. University of California College of Agriculture, Davis. *Professor of Animal Husbandry.* (2, 1936; 5, 1933)
- Gottschall, Russell Y., M.S., Ph.D. Bureau of Laboratories, Michigan Department of Health, Lansing. *Bacteriologist.* (6, 1939)
- Goudsmit, Arnoldus, Jr., M.D., Ph.D. 40 Roberts Avenue, Glenside, Pa. Medical Corps, 232 General Hospital, Camp Barkeley, Texas. (1, 1940)
- Govier, William M., M.D. Sharp and Dohme, Inc., Glenolden, Pa. *Pharmacologist—Medical-Research Division.* (3, 1944)
- Grabfield, G. Philip, M.D. 27 Forest St., Milton, Mass. *Associate in Medicine and Pharmacology, Harvard Medical School.* (At present on leave of absence; Col. M.C., U. S. A.) (3, 1923)
- Grady, Hugh G., M.D. Fitzgerald-Mercy Hospital, Darby, Pa. *Director of Laboratories.* (4, 1940)
- Grace, Irving, M.D. New York University College of Medicine, New York City. *Associate Professor of Pathology; Pathologist, Bellevue Hospital and New York University Clinic.* (4, 1941)
- Graham, Clarence H., Ph.D. Columbia University, New York 27, N. Y. *Professor of Psychology.* (1, 1933)
- Graham, Helen Tredway, A.M., Ph.D. Euclid Ave. and Kingshighway, St. Louis, Mo. *Associate Professor of Pharmacology, Washington University School of Medicine.* (1, 1933; 3, 1931)
- Grant, R. Lorimer, M.S., Ph.D. Division of Pharmacology, Food and Drug Administration, Federal Security Agency, Washington 25, D. C. *Pharmacologist.* (2, 1938)
- Graubard, Mark, M.A., Ph.D. 3427 Oakwood Ter., N. W., Washington, D. C. (1, 1940)
- Grauer, Robert C., M.D. Allegheny General Hospital, Pittsburgh, Pa. *Head of Department of Research in Endocrinology and Metabolism, William H. Singer Memorial Research Laboratory; Lecturer in Pathology, School of Medicine, University of Pittsburgh.* (4, 1941)
- Gray, John S., M.S., Ph.D. Research Division, School of Aviation Medicine, Randolph Field, Texas. *Assistant Professor of Physiology, Northwestern University Medical School, Chicago, Ill. (on leave).* (1, 1937)
- Gray, Samuel H., M.D. The Jewish Hospital of St. Louis, Kingshighway and Forest Park Blvd., St. Louis, Mo. *Pathologist, Jewish Hospital; Director of Laboratories, City Hospitals; Associate Professor of Pathology, Washington University.* (4, 1939)
- Greaves, J. D., M.S., Ph.D. Western Regional Research Lab., U. S. Dept. of Agriculture, 800 Buchanan St., Albany 6, Calif. *Biochemist.* (2, 1938)
- Greaves, Joseph E., Ph.D. Utah State Agricultural College, Logan. *Professor and Head of Department of Bacteriology and Biochemistry.* (2, 1940)
- Grceley, Paul O., A.M., Ph.D., M.D. University of Southern California Medical School, University Park, Los Angeles. *Dept. of Aviation Medicine.* (1, 1940)
- Green, Arda Alden, M.D. Cleveland Clinic, Euclid and E. 93rd St., Cleveland 6, O. *Research Division.* (2, 1932)
- Green, Daniel M., M.D. Kings County Hospital, Seattle, Wash. *Instructor, Pharmacology and Therapeutics, University of Tennessee (on leave). Lt. Col. 0-291885, M.C.* (3, 1942)
- Green, David E., Ph.D. Department of Medicine, College of Physicians and Surgeons, Columbia University, New York City. *Associate in Biochemistry.* (2, 1941)

- Green, Harold David, M.D.** Bowman Gray School of Medicine, Wake Forest College, Winston-Salem 7, N. C. *Professor of Physiology and Pharmacology.* (1, 1936; 3, 1945)
- Green, Robert, M.A., M.D.** 223 Millard Hall, University of Minnesota, Minneapolis. *Professor of Bacteriology and Immunology.* (6, 1930)
- Greenberg, David Morris, Ph.D.** University of California, Berkeley. *Professor of Biochemistry.* (2, 1927)
- Greene, Carl Hartley, Ph.D., M.D.** 401 Clinton Ave., Brooklyn, N. Y. *Associate Professor of Clinical Medicine, New York Post-Graduate Medical School of Columbia University; Clinical Professor of Medicine, Long Island College of Medicinc.* (1, 1921; 2, 1922; 4, 1924)
- Greene, Charles Wilson, A.M., Ph.D.** 814 Virginia Ave., Columbia, Mo. *Lecturer in Physiology, Stanford University; Professor Emeritus of Physiology and Pharmacology, University of Missouri.* (1, 1900; 2, 1919; 3, 1909)
- Greene, Harry S. N., M.D., C.M.** Department of Pathology, Yale University School of Medicine, New Haven, Conn. *Professor of Pathology.* (4, 1937)
- Greene, James Alexander, M.D.** Baylor University, College of Medicine, Buffalo Drive., Houston, Texas. *Professor and Chairman of the Department of Internal Medicine and Dean of the Clinical Faculty.* (1, 1939)
- Greene, Ronald R., M.S., M.D.** Northwestern University Medical School, 303 E. Chicago Ave., Chicago, Ill. *Instructor in Physiology; Instructor in Obstetrics and Gynecology.* (1, 1941)
- Greengard, Harry, Ph.D., M.D.** Northwestern University Medical School, 303 E. Chicago Ave., Chicago, Ill. *Assistant Professor of Physiology.* (1, 1939)
- Greenstein, Jesse P., Ph.D.** National Cancer Institute, Bethesda, Md. *Senior Biochemist.* (2, 1935)
- Greenwald, Isidor, Ph.D.** 477 First Ave., New York City. *Associate Professor of Chemistry, New York University College of Medicine.* (2, 1912; 5, 1933)
- Greep, Roy O., Ph.D.** Squibb Inst. for Medical Research, New Brunswick, N. J. *Research Associate in Pharmacology.* (1, 1940)
- Greer, C. M., M.S.** Vanderbilt University School of Medicine, Nashville, Tenn. *Research Associate in Pharmacology.* (3, 1938)
- Gregersen, Magnus I., A.M., Ph.D.** College of Physicians and Surgeons, Columbia University, 630 W. 168th St., New York City. *Professor of Physiology.* (1, 1933)
- Gregg, Donald Eaton, M.S., Ph.D.** University of Rochester Medical School, 260 Crittenden Blvd., Rochester 7, N. Y. (1, 1933)
- Gregory, Raymond L., Ph.D., M.D.\*** University of Texas School of Medicine, 1419—24th St., Galveston. *Professor of Medicinc.* (1, 1945)
- Greisheimer, Esther M., Ph.D., M.D.** Temple University Medical School, 3400 N. Broad St., Philadelphia, Pa. *Professor of Physiology.* (1, 1925)
- Grenell, Robert G., Ph.D.\*** Section of Neuro-anatomy, Yale University School of Med., New Haven 11, Conn. *Research Assistant (rank of Instructor), Laboratory of Physiology.* (1, 1945)
- Griffin, Angus, Ph.D.** Department of Bacteriology, George Washington University School of Medicine, 1335 H St., N.W., Washington, D. C. *Assistant Professor of Baeteriology.* (6, 1940)
- Griffith, Fred R., Jr., M.A., Ph.D.** 24 High St., Buffalo, N. Y. *Professor of Physiology, University of Buffalo Medical School.* (1, 1923; 5, 1933)
- Griffith, Wendell H., M.S., Ph.D. Sn.C., 0-426073, APO #887, c/o P. M., New York City. Colonel, Office Chief Surgeon, USFET (Rear). Chief of Nutrition Branch.** (2, 1923; 5, 1934)
- Grimson, Keith S., M.D.\*** Duke University School of Medicine, Durham, N. C. *Associate Professor of Surgery.* (1, 1943)
- Grindlay, John H., M.D.\*** Mayo Clinic, Rochester, Minn. (1, 1945)
- Groat, Richard A., Ph.D.\*** Northwestern University Medical School, 303 E. Chicago Ave., Chicago 11, Ill. *Assistant Professor of Neurology.* (1, 1945)
- Groat, William A., M.D.** 713 E. Genesee St., Syracuse, N. Y. *Professor of Clinical Pathology, Syracuse University College of Medicine.* (6, 1917)
- Grodins, Fred S., M.D.\*** School of Aviation Medicine, Randolph Field, Texas. *Captain, M.C.* (1, 1945)
- Grollman, Arthur, M.D., Ph.D.** Southwestern Medical College, 2211 Oak Lawn Ave., Dallas, Texas. *Professor of Experimental Medicine and Lecturer in Physiology and Pharmacology.* (1, 1928; 3, 1933)
- Gross, Erwin G., Ph.D., M.D.** Medical Laboratories, State University of Iowa, Iowa City. *Professor of Pharmacology.* (1, 1927; 2, 1923; 3, 1927)
- Gross, Robert E., M.D.** Harvard Medical School, 300 Longwood Ave., Boston, Mass. *Assistant Professor of Surgery.* (4, 1940)
- Gruber, Charles M., A.M., M.D., Ph.D.** Jefferson Medical College, 1025 Walnut St., Philadelphia, Pa. *Professor of Pharmacology.* (1, 1914; 3, 1919)
- Gruhzit, Oswald M., M.D.** Research Laboratories, Parke, Davis & Co., Detroit, Mich. *Research in Pathology and Pharmacology.* (4, 1928)

- Grundfest, Harry, A.M., Ph.D. Columbia Univ. P. and S., 630 West 168th St., New York 32, N. Y. *Associate in Neurology.* (1, 1932)
- Gudernatsch, F., Ph.D. Graduate School, New York University, Washington Square E., New York City. *Visiting Professor.* (1, 1930)
- Guerrant, N. B., M.S., Ph.D. Pennsylvania State College, State College. *Professor of Biological Chemistry.* (2, 1934; 5, 1933)
- Guest, George Martin, M.S., M.D. The Children's Hospital, Research Foundation, Elland and Bethesda Aves., Cincinnati, O. *Fellow of the Children's Hospital Research Foundation; Associate Professor of Pediatrics, University of Cincinnati, College of Medicine and Graduate School.* (2, 1933)
- Gulick, Addison, A.M., Ph.D. 308 Westmount Ave., Columbia, Mo. *Professor of Physiological Chemistry, University of Missouri.* (1, 1915; 5, 1933)
- Gunn, Francis D., M.D. University of Utah, School of Medicine, Salt Lake City. *Professor of Pathology.* (4, 1938)
- Gurin, S., M.S., Ph.D. University of Pennsylvania School of Medicine, Philadelphia. *Assistant Professor in Physiological Chemistry.* (2, 1938)
- Gustavson, Reuben G., Ph.D. University of Chicago, Chicago 37, Ill. *Dean of Faculties.* (2, 1927)
- Gustus, Edwin L., M.Sc., Ph.D. Benning Hall, 3445 38th St., N.W., Washington 16, D. C. *Research and Development Branch, Military Planning Division, OQMG, War Department, Director of Research.* (2, 1934)
- Guthrie, Charles Claude, M.D., Ph.D., Sc.D. University of Pittsburgh Medical School, Pittsburgh, Pa. *Professor of Physiology and Pharmacology.* (1, 1905; 3, 1909)
- de Gutierrez-Mahoney, C. G., M.D. St. Vincent's Hospital, New York, N. Y. (1, 1940; 4, 1941)
- György, Paul, M.D. 3400 Spruce St., Philadelphia 4, Pa. *Associate Research Professor of Pediatrics, University of Pennsylvania School of Medicine.* (2, 1938; 5, 1939)
- Haag, Harvey B., M.D. Medical College of Virginia, Richmond. *Professor of Pharmacology.* (3, 1934)
- Haag, J. R., Ph.D. Oregon Agricultural Experiment Station, Corvallis. *Chemist.* (5, 1941)
- Haberman, Sol, M.A., Ph.D. Baylor University Hospital, Dallas, Texas. *Assistant Professor Clinical Pathology, Serologist.* (6, 1944)
- Hadidian, Zareh, Ph.D.\* Worcester State Hospital, Worcester, Mass. *Physiologist, Memorial Foundation for Neuro-endocrine Research.* (1, 1945)
- Hadley, Philip Bardwell, Ph.D. Institute of Pathology, Western Pennsylvania Hospital,
- Pittsburgh. *Chief of Bacteriological Service and Research Bacteriologist.* (4, 1927)
- Haskesbring, H. Roberta, Ph.D. Woman's Medical College of Pennsylvania, East Falls, Philadelphia. *Professor of Physiology.* (1, 1931)
- Haggard, Howard W., M.D. 4 Hillhouse Ave., New Haven, Conn. *Director of the Laboratory of Applied Physiology, Yale University.* (1, 1919; 2, 1920)
- Hahn, Paul F., Ph.D. Vanderbilt University School of Medicine, Nashville, Tenn. *Associate Professor of Biochemistry.* (4, 1939)
- Haig, Charles, M.A., Ph.D. New York Medical College, Flower and Fifth Avenue Hospital, Fifth Ave. at 105th St., New York City. *Assistant Professor of Physiology.* (1, 1942)
- Haist, Reginald E., M.A., M.D., Ph.D.\* University of Toronto, Toronto, Ontario, Canada. *Associate Professor of Physiology.* (1, 1943)
- Haldi, John, A.M., Ph.D. Emory University, Atlanta, Ga. (1, 1928)
- Hale, Worth, M.D. Harvard Medical School, Boston, Mass. *Associate Professor of Pharmacology.* (1, 1908; 3, 1908)
- Hale, Wm. M., M.D. The State University of Iowa College of Medicine, Iowa City. *Professor of Bacteriology.* (4, 1941; 6, 1935)
- Hall, F. G., M.A., Ph.D. Lt. Col., Aero-Medical Laboratory, Wright Field, Dayton, O. (1, 1937)
- Hall, George Edward, M.D., Ph.D. University of Western Ontario, Ottawa Ave. and Waterloo St., London, Canada. *Dean of the Faculty of Medicine.* (1, 1938)
- Hall, Victor E., M.A., M.D. Department of Physiology, Stanford University, Calif. *Professor of Physiology.* (1, 1934)
- Halliday, Nellie, Ph.D. Research Laboratory, Mt. Zion Hospital, San Francisco, Calif. (5, 1933)
- Halpert, Béla, M.D. University of Oklahoma School of Medicine, Oklahoma City. *Director of Laboratories and Professor of Clinical Pathology.* (4, 1936)
- Halsey, John T., M.D. P. O. Box 264, Waveland, Miss. *Professor Emeritus of Pharmacology, Tulane University of Louisiana.* (3, 1929)
- Halstead, Ward C., M.A., Ph.D. Dept. of Medicine, University of Chicago, Chicago, Ill. *Associate Professor Experimental Psychology, Division of Psychiatry.* (1, 1942)
- Ham, Arthur W., M.B. University of Toronto, Toronto 5, Canada. *Professor of Anatomy, in charge of Histology.* (4, 1939)
- Hamberger, Walter E., Ph.D., M.D. G. D. Searle & Co., P. O. Box 5110, Chicago, Ill. *Chief Pharmacologist.* (3, 1934)
- Hamilton, Bengt L. K., M.D. U. S. Marine Hospital, Staten Island, N. Y. *Senior Surgeon,*

- Hegnauer, Albert H., Ph.D. Syracuse University, Syracuse, N. Y. Assistant Professor of Physiology. (1, 1937)
- Hegsted, David Mark, M.S., Ph.D. Schools of Medicine & Public Health, Harvard University, 25 Shattuck St., Boston, Mass. Associate in Nutrition. (5, 1944)
- Heidelberger, Michael, Ph.D., M.A. 620 W. 168th St., New York City. Professor of Biological Chemistry, Columbia University; Chemist to the Medical Service, Presbyterian Hospital. (2, 1927; 6, 1935)
- Heilbrunn, Lewis Victor, Ph.D. University of Pennsylvania, Philadelphia. Professor of Zoology. (1, 1930)
- Heim, J. William, Ph.D. Aero-Medical Laboratory, Army Air Forces, Wright Field, Dayton, O. Principal Research Physiologist; Assistant in Physiology, Harvard School of Public Health (1, 1936)
- Heinbecker, Peter, M.D. Washington University Medical School, St. Louis, Mo. Associate Professor of Surgery. (1, 1930)
- Helff, O. M., M.S., Ph.D. New York University, University Heights, New York City. Associate Professor of Biology. (1, 1932)
- Hellbaum, Arthur A., M.A., Ph.D., M.D. University of Oklahoma School of Medicine, Oklahoma City. Professor of Pharmacology. (1, 1937; 3, 1945)
- Hellebrandt, Frances Anna, M.D. Medical College of Virginia, Richmond. Professor of Physical Medicine. (1, 1933)
- Heller, Carl G., M.D., Ph.D.\* University of Oregon Medical School, Portland 1. Associate Professor of Physiology and Medicine. (1, 1945)
- Heller, Victor G., Ph.D. Oklahoma A. & M. College, Stillwater. Head of the Department of Agricultural Chemistry Research. (2, 1935; 5, 1935)
- Hellerman, Leslie, Ph.D. Johns Hopkins University School of Medicine, 710 N. Washington St., Baltimore, Md. Assistant Professor Physiological Chemistry. (2, 1935)
- Helmer, Oscar Marvin, M.S., Ph.D. Lilly Laboratory for Clinical Research, The Indianapolis City Hospital, Indianapolis, Ind. Head of Department of Physiological Chemistry; Research Associate in the Department of Medicine, Indiana University School of Medicine. (2, 1935)
- Hemingway, Allan, Ph.D. 210 Millard Hall, University of Minnesota, Minneapolis. Assistant Professor of Physiological Chemistry; Temporarily at School of Aviation Medicine, Randolph Field, Texas. (1, 1933)
- Hendrix, Byron M., Ph.D. School of Medicine, University of Texas, Galveston. Professor of Biochemistry. (2, 1920)
- Hendrix, James Paisley, M.A., M.D. Duke Hospital, Durham, N. C. Associate in Medicine (in charge of Therapeutics); Associate in Physiology and Pharmacology, Duke University School of Medicine. (3, 1942)
- Hendry, Jessie L., M.A. Division of Laboratories and Research, New York State Department of Health, New Scotland Ave., Albany. Senior Bacteriologist. (6, 1938)
- Henle, Werner, M.D. University of Pennsylvania, Philadelphia. Assistant Professor of Bacteriology in Pediatrics. (6, 1938)
- Henschel, Austin F., Ph.D.\* University of Minnesota, Minneapolis. Physiologist, U. S. War Dept. (QMC), and Instructor in Physiology, University of Minnesota. (1, 1944)
- Hepburn, Joseph Samuel, A.M., M.S., Ph.D., M.D. 235 N. 15th St., Philadelphia 2, Pa. Professor of Chemistry and Research Associate in Gastro-Enterology, Hahnemann Medical College and Hospital. (2, 1915)
- Hepler, Opal E., Ph.D., M.D. Northwestern University Medical School, 303 E. Chicago Ave., Chicago, Ill. Assistant Professor of Pathology. (4, 1939)
- Herbst, R. M., Ph.D. 39 Knollwood Road, Short Hills, N. J. Director of Research, E. Bilhuber, Inc., Orange, N. J. (2, 1938)
- Herrick, C. Judson, Ph.D. 236 Morningside Drive, Grand Rapids, Mich. Professor Emeritus of Neurology, University of Chicago; Member of the National Academy of Sciences. (1, 1907)
- Herrick, Julia F., M.A., Ph.D. 175 Chelsea Ave., Long Branch, N. J. Mayo Foundation, Rochester, Minn. (1, 1933)
- Herrin, Raymond C., Ph.D., M.D. University of Wisconsin Medical School, Madison. Associate Professor of Physiology. (1, 1932)
- Herrington, Lovie P., M.A., Ph.D. 290 Congress Ave., New Haven, Conn. Associate Director, John B. Pierce Laboratory of Hygiene; Research Associate Professor, Dept. of Public Health, Yale Medical School. (1, 1942)
- Herriott, Roger M., Ph.D. Rockefeller Institute for Medical Research, Princeton, N. J. Associate. (2, 1940)
- Herrman, George, Ph.D., M.D. University of Texas, Medical Branch, Galveston. Professor of Medicine. (4, 1925)
- Herrmann, Julian B., M.D. Yale School of Medicine, New Haven, Conn. Research Assistant in Pharmacology. (3, 1941)
- Herrmann, Louis George, M.D. Cincinnati General Hospital, Cincinnati 29, O. Associate Professor of Surgery, University of Cincinnati College of Medicine; Assistant Director of Surgical Services, Cincinnati General Hospital and Children's Hospital. (4, 1933)

- Hershey, A. D., Ph.D. Washington University School of Medicine, St. Louis, Mo. *Assistant Professor of Bacteriology and Immunology.* (6, 1942)
- Hertig, Arthur T., M.D. Harvard University Medical School, 221 Longwood Ave., Boston, Mass. *Assistant Professor of Pathology and Assistant Professor of Obstetrics.* (4, 1941)
- Hertz, Roy, Ph.D., M.D.\* National Institute of Health, Bethesda 14, Md. *P. H. Surgeon (R), Division of Physiology.* (1, 1945)
- Hertz, Saul, M.D. Massachusetts General Hospital, Fruit St., Boston. *Research Associate, Harvard Medical School and Massachusetts Institute of Technology.* (4, 1935)
- Hertzman, Alrick B., Ph.D. St. Louis University School of Medicine, St. Louis, Mo. *Professor of Physiology and Director of the Department.* (1, 1925)
- Herwick, Robert P., Ph.D., M.D., LL.B. U. S. Food and Drug Administration, Washington, D. C. *Chief, Drug Division, Associate Prof. Pharmacology, Georgetown Medical School, Adjunct Clinical Professor Medicine (Therapeutics) George Washington Medical School.* (3, 1938)
- Hess, Charles L., M.S., M.D. 308 Davidson Bldg., Bay City, Mich. (1, 1916)
- Hess, Walter C., Ph.D. Chemo-Medical Research Institute, Georgetown University, Washington, D. C. *Associate Research Professor.* (2, 1935)
- Hetherington, Albert W., M.S., Ph.D.\* Northwestern University Medical School, 303 E. Chicago Ave., Chicago, Ill. *Instructor in Neurology.* (1, 1943)
- Hewitt, Earl Albon, M.S., Ph.D. Iowa State College, Ames. *Associate Professor of Veterinary Physiology.* (1, 1932)
- Hewitt, Julia A. W., B.A. Nassau Hospital, Mineola, N. Y. *Senior Technician, in charge.* (6, 1921)
- Heyroth, Francis F., M.D., Ph.D. Kettering Laboratory, College of Medicine, University of Cincinnati, Cincinnati, O. *Assistant Professor of Applied Physiology.* (2, 1935)
- Hiatt, Edwin P., M.A., Ph.D. North Carolina University School of Medicine, Chapel Hill. *Associate Professor of Physiology.* (1, 1942)
- Hickman, Kenneth C. D., Ph.D. Distillation Products, Inc., 755 Ridge Road W., Rochester, N. Y. *Vice-President and Director of Research.* (2, 1944)
- Higgins, Harold Leonard, M.D. 322 Franklin, Newton, Mass. *Assistant Professor of Pediatrics, Harvard University.* (1, 1914; 5, 1933)
- Hill, Edgar S., M.S., Ph.D. Washington University, College of Dentistry, St. Louis, Mo. *Associate Professor of Biological Chemistry and Physiology.* (2, 1936)
- Hill, Robert M., M.S., Ph.D. 4200 E. 9th Ave., Denver, Colo. *Associate Professor of Biochemistry, University of Colorado Medical School.* (2, 1933)
- Hill, Samuel E., M.A., Ph.D. 18 Collins Ave., Troy, N. Y. *Research Worker, The Behr-Manning Corp.* (1, 1934)
- Hiller, Alma, Ph.D. Rockefeller Institute for Medical Research, 66th St. and York Ave., New York City. *Associate.* (2, 1929)
- Himmelsbach, C. K., M.D. U. S. Public Health Service, 1061 Dierks Building, Kansas City 6, Mo. *Surgeon, U. S. P. H. S.* (3, 1938)
- Himwich, Harold E., M.D. Albany Medical College, Albany, N. Y. *Professor of Physiology and Pharmacology.* (1, 1925; 5, 1933)
- Hines, Harry M., M.S., Ph.D. The State University of Iowa, Iowa City. *Professor of Physiology.* (1, 1928)
- Hines, Marion, Ph.D. Johns Hopkins Medical School, Baltimore, Md. *Associate Professor of Anatomy.* (1, 1932)
- Hinrichs, Marie, Ph.D. Southern Illinois Normal University, Carbondale. *Professor of Physiology; Director of Student Health Service.* (1, 1928)
- Hinsey, Joseph C., M.S., Ph.D. Cornell University Medical College, 1300 York Ave., New York City. *Professor of Anatomy and Dean of the Medical College.* (1, 1929)
- Hisaw, Frederick L., A.M., Ph.D. The Biological Laboratories, Harvard University, Cambridge Mass. *Professor of Zoology.* (1, 1932)
- Hitchcock, David I., Ph.D. 333 Cedar St., New Haven, Conn. *Associate Professor of Physiology, Yale University.* (2, 1930)
- Hitchcock, Fred A., M.Sc., Ph.D. Ohio State University, Columbus. *Professor of Physiology.* (1, 1927; 5, 1933)
- Hitchings, George H., M.S., Ph.D. 50 Primrose Ave., Tuckahoe 7, N. Y. *Biochemist, Wellcome Research Laboratories.* (2, 1942)
- Hjort, Axel M., M.D., Ph.D. P. O. Box 281, 14 Fern Way, Scarsdale, N. Y. *Adjunct Physician, Grasslands Hospital, Valhalla, N. Y.* (2, 1925)
- Hoagland, Charles L., M.D. Rockefeller Institute, 66th St. and York Ave., New York City. *Associate Member.* (5, 1945)
- Hoagland, Hudson, M.S., Ph.D. Worcester State Hospital, Worcester, Mass. (1, 1932)
- Höber, Rudolf. University of Pennsylvania Medical School, Philadelphia. *Visiting Professor of Physiology.* (1, 1936)
- Hodes, Robert, Ph.D. Johnson Foundation, University of Pennsylvania, Philadelphia. *Associate in Biophysics.* (1, 1941)
- Hodge, Harold C., Ph.D. University of Rochester School of Medicine and Dentistry, Rochester,

- N. Y. Associate Professor of Biochemistry and Pharmacology. (2, 1937)
- Hoefer, Paul F. A., Ph.D., M.D.\* Neurological Institute of New York, 710 W. 168th St., New York 32, N. Y. Associate Professor of Neurology (1, 1945)
- Hoff, Ebbe Curtis, M.A., Ph.D. Department of Physiology, Yale University School of Medicine, 333 Cedar St., New Haven, Conn. (1, 1933)
- Hoff, Hebbel E., M.A., Ph.D. McGill University, Montreal, Quebec, Canada. Professor of Physiology. (1, 1933)
- Hoffman, Olive, M.S., Ph.D. Presbyterian Hospital, 51 N. 39th St., Philadelphia, Pa. (1, 1935)
- Hoffman, William Samuel, Ph.D., M.D. 629 S. Wood St., Chicago, Ill. Acting Director of Laboratories and Acting Director of the Hektoen Institute for Medical Research, Cook County Hospital. (2, 1935)
- Hogan, Albert G., A.M., Ph.D. 105 Schweitzer Hall, Columbia, Mo. Professor of Animal Nutrition, University of Missouri. (2, 1916; 5, 1933)
- Hogness, Thorfin R., Ch.E., Ph.D. Department of Chemistry, University of Chicago, Chicago, Ill. Professor of Chemistry. (2, 1941)
- Holck, Harald G. O., Ph.D. College of Pharmacy, University of Nebraska, Lincoln. Associate Professor of Pharmacology. (1, 1935; 3, 1938)
- Hollander, Franklin, Ph.D. Mount Sinai Hospital, Fifth Ave. and 100th St., New York City. Associate in Physiology; Head, Gastro-Enterology Research Laboratory. (1, 1942; 2, 1932)
- Holman, Russell Lowell, M.D. University of North Carolina School of Medicine, Chapel Hill. Professor of Pathology. (4, 1940)
- Holmes, Arthur Dunham, Ph.D. Massachusetts State College, Amherst. Research Professor of Chemistry. (2, 1931; 5, 1933)
- Holmes, Julia O., M.S., Ph.D. Massachusetts State College, Amherst. Research Professor of Nutrition. (2, 1942; 5, 1936)
- Holt, Joseph Paynter, M.S., M.D., Ph.D. Standard Oil Co., Room 2400, 30 Rockefeller Plaza, New York 20, N. Y. Director of Medical Research. (1, 1942)
- Holt, L. Emmett, Jr., M.D. 477 First Ave., New York 16, N. Y. Professor of Pediatrics, New York University College of Medicine. (2, 1930)
- Hoobler, Icie Macy, Ph.D., D.Sc. 660 Frederick St., Detroit, Mich. Director of Research, Children's Fund of Michigan; Associate in Nutrition, Medical Staff of the Children's Hospital of Michigan. (2, 1925; 5, 1933)
- Hooker, Davenport, M.A., Ph.D. University of Pittsburgh School of Medicine, Pittsburgh, Pa. Professor of Anatomy. (1, 1920)
- Hooker, Donald R., M.S., M.D. 19 W. Chase St., Baltimore, Md. Lecturer in Physiological Hygiene, School of Hygiene and Public Health, Johns Hopkins University; Managing Editor of American Journal of Physiology, Physiological Reviews and Federation Proceedings. (1, 1906; 3, 1911)
- Hooker, Sanford B., A.M., M.D. 80 E. Concord St., Boston, Mass. Member, Evans Memorial. (6, 1918)
- Hoppert, C. A., Ph.D. Michigan State College, Box 626, East Lansing. Professor of Biological Chemistry. (5, 1935)
- Horsfall, Frank L., Jr., M.D., C.M. Rockefeller Institute, 66th St. and York Ave., New York City. Member. (6, 1937)
- Horvath, Steven M., M.A., Ph.D.\* Armored Forces Medical Research Laboratory, Ft. Knox, Ky. Major, San. Corps. (1, 1943)
- Horwitt, M. K., Ph.D. Biochemical Research Laboratory, Elgin State Hospital, Elgin, Ill. Director, Biochemical Research Laboratory; Assistant Professor, Physiological Chemistry, University of Illinois School of Medicine. (2, 1941)
- Hoskins, R. G., Ph.D., M.D. Harvard Medical School, Boston, Mass. Research Associate in Physiology, Harvard University; Director of Research, Memorial Foundation for Neuroendocrine Research. (1, 1911)
- Hotchkiss, Rollin D., Ph.D. The Rockefeller Institute for Medical Research, 66th St. and York Ave., New York City. Lieut. Commander, Hospital Corps, USNR. (2, 1941)
- Howard, Evelyn, A.M., Ph.D. Johns Hopkins School of Medicine, Baltimore, Md. Instructor in Physiology. (1, 1933)
- Howard, Marion E., M.D. New Haven Hospital, New Haven, Conn. Assistant Professor of Medicine, Yale School of Medicine; Associate Physician, New Haven Hospital and New Haven Dispensary. (4, 1939; 6, 1937)
- Howe, Paul E., A.M., Ph.D. 2823 29th St. N.W., Washington, D. C. Colonel, Sanitary Corps; Chief, Nutrition Branch, Office of the Surgeon General, U. S. Army. On leave as Chief, Animal Nutrition Division, and Assistant Chief, Bureau of Animal Industry, U. S. Department of Agriculture. (1, 1913; 2, 1909; 5, 1933)
- Howe, Percy R., M.D., D.D.S. Harvard Medical School, Boston, Mass. Director Forsyth Dental Infirmary; Professor Dental Sciences; Instructor in Pathology. (5, 1935)
- Howell, Katherine M., M.D. Michael Reese Hospital, 2900 Ellis Ave., Chicago, Ill. Head of Departments of Bacteriology and Serology. (6, 1940)
- Howell, Stacey F., Ph.D. V. D. Research Laboratory, U. S. Marine Hospital, Stapleton, Staten

- Island, N. Y. *Chemist, U. S. Public Health Service.* (2, 1940)
- Hubbard, Roger Sanford, A.M., Ph.D. 37 Berkly Place, Buffalo 9, N. Y. *Biochemist, Buffalo General Hospital; Professor of Physiology, Buffalo University Medcial School.* (1, 1922; 2, 1920).
- Hubbell, Rebecca B., M.S., Ph.D. Connecticut Agricultural Experiment Station, New Haven. *Assistant Biochemist.* (2, 1937; 5, 1935)
- Hudack, Stephen Sylvester, M.D. 180 Fort Washington Ave., New York, N. Y. *Associate Professor of Orthopedic Surgery, Columbia Univ.* (4, 1933)
- Huddleston, Ora Leonard, M.D., Ph.D. Fitzsimmons General Hospital, Denver, Colo. *Major, MC; Instructor in Physiology, University of Colorado School of Medicinc.* (1, 1936)
- Hueper, Wilhelm C., M.D. Warner Institute for Therapeutic Research, 113 W. 18th St., New York City. *Assistant Director and Principal Pathologist.* (4, 1940)
- Huffman, C. F., M.S., Ph.D. Michigan State College, East Lansing. *Researck Professor and Associate Profcssor in Dairy Husbandry.* (5, 1937)
- Huggins, Charles Brenton, M.D. University of Chicago, Chicago, Ill. *Profcssor of Surgery.* (1, 1932)
- Hughes, Joseph, M.D. 111 N. 49th St., Philadelphia, Pa. *Assistant Professor of Experimental Neurology, Graduate School of Medicine, University of Pennsylvania; Director of Laboratory, Pennsylvania Hospital for Mental Diseases.* (1, 1936)
- Hughes, Josiah Simpson, M.A., M.S., Ph.D. Kansas State College, Manhattan. *Professor of Chemistry.* (2, 1931; 5, 1939)
- Hughes, Thomas P., A.M., Ph.D. Rockefeller Foundation, 49 W. 49th St., New York City. *Member of Staff, International Health Division.* (6, 1934)
- Hulpius, Harold R., M.A., Ph.D. Indiana University School of Medicine, Indianapolis. *Associate Professor of Pharmacology.* (3, 1939)
- Hunscher, Helen A., Ph.D. Western Reserve University, 2023 Adelbert Rd., Cleveland, O. *Head of Department of Home Economics.* (5, 1934)
- Hunt, Reid, M.D., Ph.D., Sc.D. Harvard Medical School, Boston, Mass. *Professor Emeritus of Pharmacology, Harvard University; Member, National Academy of Sciences.* (1, 1895; 2, 1906; 3, 1908)
- Hunter, Andrew, M.A., M.B., F.R.S.C. University of Toronto, Toronto, Canada. *Professor of Pathological Chemistry.* (2, 1908)
- Hunter, George, M.A., D.Sc., F.R.S.C. University of Alberta, Edmonton, Canada. *Professor of Biochemistry.* (2, 1924)
- Hunter, Jesse E., M.S., Ph.D. Allied Mills, Inc., 7500 S. Adams St., Peoria, Ill. *Director Biological Research.* (5, 1936)
- Hussey, Raymond, M.D. Homewood Apartments, Baltimore, Md. (4, 1927)
- Ingalls, Mabel S., Ph.D. 1218 Bank St., N. W., Washington 7, D. C. (6, 1940)
- Ingle, Dwight J., M.S., Ph.D. The Upjohn Co., Research Department, Kalamazoo, Mich. *Upjohn Research Fellow.* (1, 1939)
- Ingraham, Raymond Clifford, Ph.D. College of Medicine, University of Illinois, 1853 W. Polk St., Chieago. *Assistant Professor in Physiology.* (1, 1938)
- Ingram, W. R., Ph.D. College of Medicine, The State University of Iowa, Iowa City. *Professor and Head of the Department of Anatomy.* (1, 1936)
- Irvin, J. Logan, Ph.D. Johns Hopkins University School of Medicine, 710 N. Washington St., Baltimore, Md. *Assistant Professor of Physiological Chemistry.* (2, 1942)
- Irving, Laurence, A.M., Ph.D. Swarthmore College, Swarthmore, Pa. *Lt. Col., A.C. Professor of Experimental Biology.* (1, 1927)
- Irwin, M. R., Ph.D. Department of Genetics, University of Wisconsin, Madison. *Professor of Genetics.* (6, 1936)
- Isaacs, Raphael, M.D. 104 S. Michigan Ave., Suite 630, Chicago 3, Ill. *Director, Department of Hematology, Michael Reese Hospital.* (4, 1928)
- Isenberger, R. M., M.A., M.D. University of Kansas School of Medicine, Kansas City. *Professor of Pharmacology.* (3, 1937)
- Ivy, Andrew C., Ph.D., M.D. 303 E. Chicago Ave., Chicago, Ill. *Nathan Smith Davis Professor of Physiology and Professor of Pharmacology, Northwestern University Medical School.* (1, 1919; 5, 1933)
- Izquierdo, J. Joaquin, M.D. National School of Medicine, Mexico City. *Professor of Physiology in the National School of Medicine and the Escuela Medico Militar of Mexico.* (1, 1928)
- Jackson, Dennis Emerson, A.M., Ph.D.. M.D. University of Cincinnati Medical School, Eden and Bethesda Aves., Cincinnati, O. *Professor of Pharmacology.* (1, 1910; 3, 1912)
- Jackson, Eugene L., Ph.D. Emory University, Ga. *Associate Professor of Pharmacology, Chairman, Department of Pharmacology.* (3, 1942)
- Jackson, Richard W., Ph.D. Eastern Regional Research Laboratory, U. S. Department of Agriculture, Wyndmoor, Pa. *Chief of Protein Division.* (2, 1930; 5, 1933)

- Jacobs, Merkel Henry, Ph.D.** University of Pennsylvania, Philadelphia. Professor of General Physiology; Member of the National Academy of Sciences. (1, 1919)
- Jacobs, Walter A., A.M., Ph.D.** Rockefeller Institute, 66th St. and York Ave., New York City. Member; Member, National Academy of Sciences. (2, 1908; 3, 1913)
- Jacobson, Edmund, Ph.D., M.D.** Laboratory for Clinical Physiology, 55 E. Washington St., Chicago, Ill. (1, 1929)
- Jaffe, Henry L., M.D.** Hospital for Joint Diseases, 1919 Madison Ave., New York City. Director of Laboratories. (4, 1925)
- Jahn, Theodore Louis, Ph.D.\*** State University of Iowa, Iowa City. Associate Professor of Zoology. (1, 1944)
- Jamieson, Walter A., Sc.D.(hon.).** Eli Lilly & Company, Indianapolis, Ind. Director, Biological Division. (6, 1927)
- Jaques, L. B., M.A., Ph.D.\*** University of Toronto, Toronto 5, Canada. Assistant Professor, Dept. of Physiology. (1, 1943)
- Jasper, Herbert H., M.A., Ph.D., D. ès Sci.** Montreal Neurological Institute, 3801 University St., Montreal, Que., Canada. Lecturer in Neuroelectrography and Director of Department of Electrophysiology. (1, 1940)
- Jeans, P. C., M.D.** State University of Iowa, Iowa City. Professor of Pediatrics. (5, 1937)
- Jensen, H., Ph.D.** Des Bergers-Bismol Labs., 338 St. Paul St., W. Montreal, Que., Canada. Director of Research; Fellow, McGill Univ. Medical School. (2, 1929)
- Jobling, James W., M.D.** Columbia University, 630 W. 168th St., New York City. Professor of Pathology. (4, 1913)
- Jochim, Kenneth E., Ph.D.** St. Louis University School of Medicine, 1402 South Grand Blvd., St. Louis 4, Mo. Department of Physiology. (1, 1942)
- Johlin, J. M., Ph.D., D.Sc.** Vanderbilt University School of Medicine, Nashville, Tenn. Associate Professor of Biochemistry. (2, 1928)
- Johnson, Frank H., A.M., Ph.D.** Princeton University, Princeton, N. J. Assistant Professor, Dept. of Biology. (1, 1942)
- Johnson, Joseph L., Ph.D., M.D.** School of Medicine, Howard University, Washington, D. C. Professor and Head of the Department of Physiology. (1, 1934)
- Johnson, J. Raymond, Ph.D.** Long Island College of Medicine, 350 Henry St., Brooklyn, N. Y. Associate Professor of Physiology and Pharmacology. (1, 1938)
- Johnson, Marvin J., M.S., Ph.D.** University of Wisconsin, Madison. Associate Professor of Biochemistry. (2, 1941)
- Johnson, Robert E., M.D., D. Phil.\*** Harvard Fatigue Laboratory, Morgan Hall, Soldiers Field, Boston, Mass. Assistant Professor, Industrial Physiology. (1, 1944; 2, 1939)
- Johnson, Treat B., Ph.D.** Amity Road, Bethany, Westville P. O., Conn. Sterling Professor of Chemistry, Yale University; Member, National Academy of Sciences. (2, 1910)
- Johnson, Victor, Ph.D., M.D.** 5807 Dorchester Ave., Chicago, Ill. Associate Professor of Physiology; Dean of Students in the Division of Biology and the School of Medicine, University of Chicago. (1, 1933)
- Johnston, Charles G., M.S., M.D.** Wayne University College of Medicine, Detroit, Mich. Professor of Surgery. (1, 1933)
- Johnston, Margaret W., Ph.D.** Box 276, Ann Arbor, Mich. Research Associate in Internal Medicine. (2, 1930; 5, 1938)
- Jolliffe, Norman, M.D.** 39 E. 75th St., New York, N. Y. (1, 1932)
- Jones, D. Breese, Ph.D.** Bureau of Human Nutrition and Home Economics, Agricultural Research Administration, U. S. Department of Agriculture, Washington, D. C. Protein Chemist. (2, 1920; 5, 1935)
- Jones, James H., M.S., Ph.D.** School of Medicine, University of Pennsylvania, Philadelphia. Associate Professor of Physiological Chemistry. (2, 1928; 5, 1933)
- Jones, Kenneth K., M.S., Ph.D.** Northwestern University Medical School, 303 E. Chicago Ave., Chicago, Ill. Associate Professor of Physiology and Pharmacology. (1, 1936)
- Jones, Lloyd R., M.S., Ph.D.** 1402 S. Grand Blvd., St. Louis, Mo. Associate Professor and Chairman of Department of Bacteriology, St. Louis University School of Medicine. (6, 1933)
- Joslin, Elliott P., M.A., M.D.** New England Deaconess Hospital, 81 Bay State Rd., Boston, Mass. Director, George F. Baker Clinic. (5, 1933)
- Jukes, Thomas Hughes, Ph.D.** Lederle Laboratories, Pearl River, N. Y. Associate Director, Pharmaceutical Division. (2, 1935; 5, 1938)
- Jung, Frederic Theodore, Ph.D., M.D.** Northwestern University Medical School, Chicago, Ill. Assistant Professor of Physiology and Pharmacology. (1, 1930)
- Jungeblut, Claus W., M.D.** College of Physicians and Surgeons, 630 W. 168th St., New York City. Professor of Bacteriology, Columbia University. (4, 1929; 6, 1926)
- Kabat, Elvin A., A.M., Ph.D.** The Neurological Institute, 710 W. 168th St., New York 32, N. Y. Research Associate in Biochemistry, College of Physicians and Surgeons, Columbia University. and The Neurological Institute. (2, 1940; 6, 1943)

- Kabat, Herman, Ph.D., M.D. 806 Taylor St., N.W., Washington, D.C. Consultant in Neurology, Health Department, District of Columbia. (1, 1941)
- Kahn, Reuben L., Sc.D., LL.D. University of Michigan Hospital, Ann Arbor. Director of Clinical Laboratories. (4, 1934; 6, 1919)
- Kalckar, Herman M., M.D., Ph.D. Department of Nutrition and Physiology, Public Health Research Institute of the City of New York, Foot of East 15th St., New York City. Research Associate. (2, 1942)
- Kamm, Oliver, M.S., Ph.D. Research Laboratory, Parke, Davis & Co., Detroit, Mich. Scientific Director. (2, 1928)
- Karpovich, Peter V., M.D., M.P.E. School of Aviation Medicine, Randolph Field, Texas. Senior Physiologist, Research Section. (1, 1942)
- Karr, Walter G., Ph.D. Smith, Kline & French Laboratories, Delaware Ave. & Poplar St., Philadelphia 23, Pa. Director of the Research Laboratories; Assistant Professor of Physiological Chemistry, University of Pennsylvania; Consulting Biochemist to the Medical Clinic of the University Hospital, Bryn Mawr Hospital, Abington Memorial Hospital. (2, 1925)
- Karshan, Maxwell, Ph.D. Department of Biological Chemistry, Columbia University, 630 W. 168th St., New York City. Associate Professor of Biochemistry. (2, 1939)
- Karsner, Howard T., M.D. Western Reserve University, 2085 Adelbert Rd., Cleveland, O. Professor of Pathology; Director of the Institute of Pathology. (4, 1913; 6, 1925)
- Katz, Gerhard, M.D. New Mexico State Hospital, Las Vegas. Assistant Superintendent. (3, 1937)
- Katz, Louis Nelson, A.M., M.D. 2900 Ellis Ave., Chicago, Ill. Director of Cardiovascular Research, Michael Reese Hospital; Professorial Lecturer in Physiology, University of Chicago. (1, 1924)
- Katzman, Philip A., Ph.D. St. Louis University School of Medicine, 1402 S. Grand Blvd., St. Louis 4, Mo. Associate Professor of Biochemistry. (2, 1935)
- Kaulbersz, Jerzy, Ph.D.\* Wayne University College of Medicine, 1512 St. Antoine St., Detroit, Mich. Research Associate in Surgery and Research Physiology. (1, 1944)
- Kay, H. D., Ph.D., D.Sc., F.R.S. National Institute for Research in Dairying, Shinfield, near Reading, England. Director, Research Professor of Biochemistry, University of Reading. (2, 1930)
- Keeton, Robert W., M.S., M.D. University of Illinois College of Medicine, 1853 W. Polk St., Chicago. Professor of Medicine. (1, 1916; 3, 1924)
- Kehoe, Robert A., M.D. Kettering Laboratory of Applied Physiology, College of Medicine, University of Cincinnati, Eden Ave., Cincinnati, O. Research Professor of Physiology. (1, 1940)
- Keith, Norman M., M.D. Mayo Clinic, Rochester, Minn. Consulting Physician, Division of Medicine, Mayo Clinic; Professor of Medicine, Mayo Foundation, University of Minnesota. (1, 1920; 3, 1932; 4, 1924)
- Keith, T. B., Ph.D. Pennsylvania State College, State College. Assistant Professor of Animal Husbandry. (5, 1941)
- Keller, Allen D., Ph.D. Baylor College of Medicine, Houston, Texas. Professor of Physiology; Chairman of Department of Physiology and Pharmacology. (1, 1931)
- Kelsler, Raymond A., Ph.D. 17 Oxford St., Chevy Chase, 15, Md. Brig. General, U. S. Army. (4, 1932)
- Kelsey, F. Ellis, Ph.D. University of Chicago, Chicago, Ill. Research Associate (Instructor) in Pharmacology. (3, 1941)
- Kelsey, Frances Kathleen O., M.S., Ph.D. University of Chicago, Chicago, Ill. Research Assistant in Pharmacology. (3, 1941)
- Kempner, Walter, M.D. Duke University School of Medicine, Durham, N. C. Assistant Professor of Medicine. (1, 1940)
- Kendall, Edward C., M.S., Ph.D., D.Sc. 627 Eighth Ave., S.W., Rochester, Minn. Professor of Biochemistry, Mayo Foundation, University of Minnesota. (1, 1916; 2, 1913; 4, prior to 1920)
- Kendall, Forrest E., Ph.D. 240-06-53rd Ave. Douglaston, Long Island, N. Y. Assistant Professor of Biochemistry, Research Service, Columbia Division, Goldwater Memorial Hospital, Welfare Island, N. Y. (6, 1943)
- Kennard, Margaret A., M.D. Psychiatric Division, Bellevue Hospital, First Ave. & 30th St., New York City. (1, 1934)
- Kennedy, Cornelia, M.A., Ph.D. University Farm, St. Paul, Minn. Associate Professor of Agricultural Biochemistry, University of Minnesota; Assistant Chemist, Minnesota Experiment Station. (2, 1924; 5, 1934)
- Kennedy, Robert P., M.D. Knollwood Drive, R. D. 1, Rochester, N. Y. (4, 1929)
- Kenton, Harold B., Ph.D. New England Deaconess Hospital, Boston, Mass. Bacteriologist and Director of the Blood Bank. (6, 1934)
- Kenyon, Allan T., M.D. University of Chicago, Division of Biological Sciences, 950 E. 59th St., Chicago, Ill. Assistant Professor of Medicine. (3, 1940)
- Keresztesy, John C., M.A., Ph.D. Cancer Research, Mt. Sinai Hospital, Fifth Ave. and 100th St., New York 19, N. Y. (2, 1941; 5, 1945)

- Kerr, Stanley E., Ph.D. American University of Beirut, Beirut, Lebanon, Syria. *Professor of Biological Chemistry.* (2, 1937)
- Kerr, Wm. J., M.D. University of California Hospital, Third and Parnassus Aves., San Francisco. *Professor of Medicine, University of California; Physician-in-Chief, University of California Hospital.* (3, 1930)
- Kesten, Homer D., M.D. College of Physicians and Surgeons, Columbia University, New York City. *Associate Professor of Pathology.* (4, 1931)
- Kety, Seymour S., M.D. Dept. of Pharmacology, Medical School, University of Pennsylvania, Philadelphia 4. *Associate in Pharmacology, Medical School; Assistant Visiting Physician in Medicine, Philadelphia General Hospital.* (3, 1945)
- Keys, Ancel, M.A., Ph.D., D.Phil. Stadium South Tower, University of Minnesota, Minneapolis. *Professor and Director of Laboratory of Physiological Hygiene.* (1, 1939; 2, 1936)
- Khorazo, Devorah, M.D. Apt. 4G, 480 W. 187th St., New York City. *Instructor in Bacteriology, Columbia University, Eye Institute.* (6, 1936)
- Kidd, John G., M.D. Cornell University Medical College, 1300 York Ave., New York City. *Professor of Pathology; Pathologist, New York Hospital.* (4, 1938; 6, 1937)
- Kik, M. C., Ph.D. College of Agriculture, University of Arkansas, Fayetteville. *Associate Professor of Agricultural Chemistry.* (5, 1942)
- Kilborn, Leslie G., M.A., M.D., Ph.D. 47 Warren Road, Toronto, Ontario, Canada. (1, 1928)
- Killian, John Allen, A.M., Ph.D. Killian Research Laboratories, Inc., 49 W. 45th St., New York City. (2, 1921)
- King, Barry G., M.A., Ph.D. College of Physicians and Surgeons, Columbia University, 630 West 168th St., New York City. *Assistant Professor of Physiology; Lieutenant, USNR, Naval Medical Research Institute, Bethesda, Md.* (1, 1938)
- King, Charles Edwin, Ph.D. Vanderbilt University, Nashville, Tenn. *Associate Professor of Physiology.* (1, 1916)
- King, Charles Glen, Ph.D. Nutrition Foundation, Inc., Chrysler Building, New York City. *Scientific Director.* (2, 1931; 5, 1933)
- King, Jessie Luella, Ph.D. Goucher College, Baltimore, Md. *Professor of Physiology.* (1, 1914)
- King, Joseph T., M.D., Ph.D. 314 Millard Hall, University of Minnesota Medical School, Minneapolis. *Assistant Professor of Physiology.* (1, 1931)
- King, Lester, S., M.D. The Fairfield State Hospital, Newtown, Conn. *Hospital Pathologist.* (4, 1941)
- Kirk, Paul L., Ph.D. University of California, Berkeley. *Professor of Biochemistry.* (2, 1933)
- Kirkbride, Mary B., Sc.D. Division of Laboratories and Research, New York State Department of Health, Albany. *Associate Director.* (6, 1921)
- Kisch, Bruno, M.D.\* 845 West End Ave., New York City. *Professor of Biochemistry, Yeshiva University.* (1, 1943)
- Kleiber, M., D.Sc.\* University of California, Davis. *Professor of Animal Husbandry.* (1, 1943; 5, 1933)
- Klein, J. Raymond, Ph.D. University of Illinois, Neuropsychiatric Institute, 912 S. Wood St., Chicago. *Biochemist and Assistant Professor of Psychiatry and Physiological Chemistry.* (2, 1941)
- Kleiner, Israel Simon, Ph.D. New York Medical College, Flower and Fifth Avenue Hospitals, New York 29, N. Y. *Professor of Physiology and Biochemistry.* (1, 1911; 2, 1912; 3, 1912; 5, 1933)
- Kleitman, Nathaniel, A.M., Ph.D. University of Chicago, Chicago, Ill. *Associate Professor of Physiology.* (1, 1923)
- Klemperer, Friedrich Wilhelm, M.D., Massachusetts General Hospital, Boston, Mass. *Assistant in Medicine.* (2, 1941)
- Kletzien, Seymour W., M.S., Ph.D., 22 Lafayette Blvd., Williamsville, N. Y. *Biochemist.* (5, 1933)
- Kline, O. L., Ph.D. U. S. Department of Agriculture, Food and Drug Administration, Washington, D. C. *Biochemist.* (5, 1936)
- Klüver, Heinrich, Ph.D. University of Chicago, Chicago, Ill. *Professor of Experimental Psychology.* (1, 1935)
- Knoefel, Peter K., M.A., M.D. University of Louisville, 101 W. Chestnut St., Louisville, Ky. *Professor of Pharmacology.* (3, 1934)
- Knowlton, Frank P., A.M., M.D. Syracuse University College of Medicine, Syracuse, N. Y. *Professor of Physiology.* (1, 1911)
- Knowlton, Clinton G., Ph.D. Aero Medical Laboratory, Wright Field, Dayton, O. (1, 1938)
- Knudson, Arthur, Ph.D. Albany Medical College, New Scotland Ave., Albany, N. Y. *Professor of Biochemistry and Associate Dean.* (2, 1919; 5, 1936)
- Knutti, Ralph Eddy, M.D. Children's Hospital, Los Angeles, Calif. *Director of Laboratories; Assistant Professor of Pathology, University of Southern California.* (4, 1933)
- Kober, Philip A., B.S. Sherman Laboratories, Detroit, Mich. *Director of Research.* (2, 1912)
- Koch, Elizabeth M., M.A., Ph.D. 1534 E. 59th St., Chicago, Ill. (2, 1925)
- Koch, Fred Conrad, M.S., Ph.D. 1534 East 59th St., Chicago, Ill. *Director of Biochemical Research, Armour Laboratories; Professor of Bio-*

- chemistry Emeritus, University of Chicago. (2, 1912; 5, 1933)
- Kochakian, Charles D., A.M.; Ph.D. University of Rochester Medical School, 260 Crittenden Blvd., Rochester, N. Y. Assistant Professor, Dept. of Vital Economics. (1, 1942)
- Koehler, Rudolph Alfred, M.D. Box 926, Carmel, Calif. Director, Veltie Metabolic Clinic. (2, 1915)
- Koehler, Alfred E., M.D., Ph.D. 317 W. Pueblo St., Santa Barbara, Calif. Physician, Sansum Clinic, Santa Barbara Cottage Hospital. (2, 1924)
- Koehne, Martha, Ph.D. Ohio State Department of Health, 75 Eighteenth Ave., Columbus. Nutritionist. (5, 1933)
- Koeps, George F., M.D. 109 Linwood Ave., Buffalo 9, N. Y. Instructor of Medicine and Associate in Physiology, University of Buffalo. (1, 1942)
- Koerber, Walter L., Ph.D. E. R. Squibb & Sons, New Brunswick, N. J. Assistant Department Head. (6, 1943)
- Kohn, Henry I., Ph.D. Duke Medical School, Durham, N. C. Assistant Professor of Physiology and Pharmacology. (1, 1940)
- Kolmer, John A., M.S., M.D., D.P.H., Sc.D., LL.D., L.H.D. 1 Montgomery Ave., Bala-Cynwyd, Pa. Professor of Medicine, Temple University; Director, Research Institute of Cutaneous Medicine. (6, 1913)
- Komarov, Simon A., M.S., M.D., Ph.D. S. S. Fels Fund, Med. Research Laboratory, 255 S. 17th St., Philadelphia, Pa. Director of Dept. of Biochemistry. (1, 1933)
- Kopeloff, Nicholas, Ph.D. New York State Psychiatric Institute, 722 W. 168th St., New York City. Principal Research Bacteriologist, New York State Psychiatric Institute and Hospital. (6, 1937)
- Koppanyi, Theodore, Ph.D. Georgetown University, Washington, D. C. Professor of Pharmacology. (1, 1924; 3, 1935)
- Korr, Irwin M., M.A., Ph.D. Still Memorial Research Trust, Kirksville, Mo. (1, 1939)
- Kozelka, Frank L., Ph.D. Dept. of Pharmacology and Toxicology, University of Wisconsin, Madison. Assistant Professor of Toxicology. On leave. Captain, S.A.C. (3, 1939)
- Krahl, Maurice E., Ph.D. Dept. of Pharmacology, College of Physicians and Surgeons, Columbia University, 630 W. 168th St., New York City. (2, 1939)
- Krakower, Cecil Alexander, M.D. University of Illinois College of Medicine, 1853 West Polk St., Chicago. Associate Professor of Pathology. (4, 1945)
- Kramer, Benjamin, A.M., M.D. 60 Plaza St., Brooklyn, N. Y. Pediatrician-in-Chief, Brooklyn Jewish Hospital; Professor of Clinical Pediatrics, Long Island College Medical School. (1, 1915; 2, 1914)
- Kramer, Martha, Ph.D. Department of Home Economics, Yenching University, Peiping, China. Professor of Food Economics and Nutrition. (5, 1933)
- Kramer, S. D., M.D., Ph.D. 55 Mendum St., Roslindale, Mass. Virologist. (6, 1944)
- Krantz, John C., Jr., M.S., Ph.D. University of Maryland Medical School, Baltimore. Professor of Pharmacology. (3, 1937)
- Krauss, William E., Ph.D. Ohio Experiment Station, Wooster. Chief, Dairy Department. (2, 1932; 5, 1933)
- Kraybill, Henry R., M.S., Ph.D. 5720 Woodlawn Ave., Chicago 37, Ill. Professorial Lecturer, Department of Biochemistry, University of Chicago; Director, Department of Scientific Research, American Meat Institute. (2, 1942)
- Krayer, Otto, M.D. Harvard Medical School, 25 Shattuck St., Boston, Mass. Associate Professor of Comparative Pharmacology. (3, 1938)
- Krop, Stephen, Ph.D. Yale University School of Medicine, 332 Cedar St., New Haven, Conn. Instructor in Pharmacology. (3, 1944)
- Krueger, Albert Paul, M.D. Captain M.C., U.S.N.R. 3517 Life Sciences Bldg., University of California, Berkeley. Professor of Bacteriology; Commanding Officer U.S.N. Medical Research Unit No. 1, Berkeley, Calif. (4, 1930; 6, 1937)
- Krueger, Hugo M., Ph.D. Univ. of Tenn. College of Med., 874 Union Avenue, Memphis 3. Associate Professor of Pharmacology. (1, 1931; 3, 1935)
- Krumbhaar, Edward B., M.D., Ph.D. University of Pennsylvania Medical School, Philadelphia. Professor of Pathology. (1, 1914; 4, prior to 1920)
- Kruse, Harry Dayton, M.D., Sc.D. Milbank-Memorial Fund, 40 Wall St., New York City. (2, 1933)
- Krusc, Theophile K., A.M., Ph.D. University of Pittsburgh Medical School, Pittsburgh, Pa. Professor of Physiology and Pharmacology. (1, 1919; 3, 1920)
- Kubie, Lawrence S., M.D. 7 E. 81st St., New York City. Associate in Neurology, College of Physicians and Surgeons, Columbia University. (4, 1928)
- Kuhn, Harry A., M.S. 3915 Fulton St., N.W., Washington, D.C. Colonel, C.W.S., War Department; Executive Officer, C. W. Procurement District. (3, 1927)
- Kuhn, Ludwig R., Ph.D. 329 2nd St., Pitcairn, Pa. (6, 1939)
- Kunde, Margarete M., Ph.D., M.D. 30 N. Michigan Ave., Chicago, Ill. Instructor in Medicine, Northwestern University Medical School; Clinical

- Assistant in Endocrinology, Cook County Hospital.* (1, 1924)
- Kurtz, Alton C., Ph.D. Department of Biochemistry, Medical School, University of Oklahoma, Oklahoma City. *Associate Professor.* (2, 1942)
- Kydd, David M., M.D. Mary Imogene Bassett Hospital, Cooperstown, N. Y. *Associate Physician.* (5, 1934)
- Kyes, Preston, A.M., Sc.D., M.D. North Jay, Me. (6, 1918)
- Lacy, G. R., M.D. University of Pittsburgh, Pittsburgh, Pa. *Professor of Bacteriology and Immunology.* (4, 1927)
- Lamb, Alvin R., M.S., Ph.D. Experiment Station, Hawaiian Sugar Planters' Association, Honolulu. *Research Associate.* (2, 1923; 5, 1934)
- Lambert, Edward H., Ph.D., M.D.\* Mayo Aero Medical Unit, Mayo Foundation, Rochester, Minn. *Associate in Physiology.* (1, 1945)
- Lambert, Robert A., M.D. Rockefeller Foundation, 49 W. 49th St., New York City. *Associate Director for the Medical Sciences.* (4, 1922)
- Lamport, Harold, M.D.\* Yale University School of Medicine, New Haven, Conn. *Assistant Professor of Physiology.* (1, 1943)
- Lamson, Paul Dudley, M.D. Vanderbilt University Medical School, Nashville, Tenn. *Professor of Pharmacology.* (1, 1921; 3, 1915)
- Lamson, Robert W., A.M., Ph.D., M.D. Suite 810, 1930 Wilshire Blvd., Los Angeles, Calif. *Professor of Medicine and Public Health, University of Southern California School of Medicine.* (6, 1928)
- Lancefield, Rebecca C., Ph.D. 4 Kenmore Rd., Douglaston, Long Island, N. Y. *Associate Member, Rockefeller Institute for Medical Research.* (6, 1933)
- Landis, Carney, Ph.D. Psychiatric Institute and Hospital, Columbia University, 722 W. 168th St., New York City. *Principal Research Psychologist and Professor of Psychology.* (1, 1939)
- Landis, Eugene Markley, Ph.D., M.D. Department of Physiology, Harvard Medical School, 25 Shattuck St., Boston, Mass. *George Higginson Professor of Physiology.* (1, 1928)
- Lands, Alonzo M., M.A., Ph.D. Frederick Stearns and Co., 6533 Jefferson Ave., Detroit, Mich. *Director, Pharmacologic Research.* (1, 1942)
- Lange, Carl, M.D. 371 Morris St., Albany, N. Y. *Associate Bacteriologist, Divisions of Laboratories and Public Health, New York State Department of Health.* (6, 1938)
- Langley, Wilson D., Ph.D. University of Buffalo Medical School, Buffalo, N. Y. *Associate Professor of Biological Chemistry.* (2, 1937)
- Langworthy, Orthello R., M.A., M.D. Johns Hopkins Hospital, Baltimore, Md. *Associate Professor of Neurology, Johns Hopkins University.* (1, 1928)
- Larrabee, Martin G., Ph.D. Johnson Foundation, for Medical Physics, University of Pennsylvania, Philadelphia. *Assistant Professor of Biophysics.* (1, 1940)
- Larson, Edward, Ph.D. Temple University Medical School, Broad and Ontario Sts., Philadelphia, Pa. *Associate Professor of Pharmacology.* (1, 1929; 3, 1937)
- Larson, Hardy W., A.M., Ph.D. Metropolitan Life Insurance Co., Biochemical Laboratory, 1 Madison Ave., New York City. *Research Chemist.* (2, 1937)
- Larson, Paul S., Ph.D. Medical College of Virginia, Richmond. *Associate in Physiology and Pharmacology.* (1, 1939)
- Larson, W. P., M.D. University of Minnesota, Minneapolis. *Professor and Head of Department of Bacteriology and Immunology.* (6, 1917)
- Lashley, K. S., M.S., Ph.D., D.Sc. Yerkes Laboratories, Orange Park, Fla. *Research Professor of Neuropsychology, Harvard University; Director, Yerkes Laboratories of Primate Biology, Inc. Member of the National Academy of Sciences.* (1, 1923)
- Laskowski, M., Ph.D. Marquette University Medical School, Milwaukee 3, Wis. *Associate Professor of Biochemistry.* (2, 1944)
- Laug, E. P., M.A., Ph.D. Division of Pharmacology, Food and Drug Administration, Federal Security Agency, Washington 25, D. C. *Senior Pharmacologist.* (2, 1938)
- Laurens, Henry, A.M., Ph.D., LL.D. P.O. Box 157, Flat Rock, N. C. *Professor of Physiology.* (1, 1913)
- Lavine, T. F., Ph.D. Lankenau Hospital Research Institute, Philadelphia, Pa. *Research Chemist.* (2, 1938)
- Lawrence, W. Sherwood, M.D. Dept. of Pharmacology, University of Michigan, Ann Arbor. *Instructor of Pharmacology.* (3, 1944)
- Lawson, Hampden, M.D., Ph.D. University of Louisville, Louisville, Ky. *Professor of Physiology.* (1, 1933)
- Leake, Chauncey D., M.S., Ph.D. The University of Texas Medical Branch, Galveston. *Vice-President of the University of Texas in Charge of the Medical Program.* (1, 1923; 3, 1924)
- Leathem, James H., Ph.D.\* Rutgers University, New Brunswick, N. J. *Assistant Professor of Zoology.* (1, 1945)
- Leathes, John Beresford, M.A., M.B., F.R.C.S., F.R.S. 106 Banbury Rd., Oxford, England. (2, 1909)

- Lederer, Ludwig George, Ph.D., M.D. Pennsylvania Central Airlines, National Airport, Washington, D. C. *Medical Director.* (1, 1940)
- Lee, Milton O., M.A., Ph.D. Harvard Medical School, Boston, Mass. *Associate, Memorial Foundation for Neuro-endocrine Research; Research Fellow in Physiology.* (1, 1927; 5, 1933)
- Lee, Robert Cleveland, B.Ch.E., M.A.\* 309 Bellevue St., Newton, Mass. *Member of Research Staff, Nutrition Lab., Carnegie Institution of Washington.* (1, 1944; 5, 1940)
- Leese, Chester E., M.S., Ph.D. George Washington University School of Medicine, Washington, D. C. *Associate Professor of Physiology.* (1, 1934)
- Lehman, Arnold J., Ph.D., M.D. University of North Carolina School of Medicine, Chapel Hill. *Professor of Pharmacology.* (3, 1937)
- Lehman, Robert A., M.S., Ph.D. New York University College of Medicine, 477 First Ave., New York City. *Instructor in Therapeutics.* (3, 1942)
- Lehmann, Gerhard, M.D., Dr.Ing. Hoffmann-La Roche, Scientific Dept., Nutley 10, N. J. *Pharmacologist.* (3, 1939)
- Lénhart, Carl H., M.D. Lakeside Hospital, 2065 Adelbert Rd., Cleveland, O. *Oliver H. Payne Professor of Surgery, Western Reserve University.* (1, 1921)
- Lennette, Edwin H., Ph.D., M.D. 49 W. 49th St. New York, N. Y. *Staff Member, International Health Division, The Rockefeller Foundation.* (4, 1941)
- Leonard, Clifford Shattuck, M.S., Ph.D. University of Vermont Medical College, Burlington. *Assistant Professor of Pharmacology.* (3, 1927)
- Lepkovsky, Samuel, M.S., Ph.D. University of California, Berkeley. *Associate Professor of Poultry Husbandry.* (2, 1933; 5, 1933)
- L'Esperance, Elise L., M.D. 321 E. 15th St., New York City. *Director of Laboratories, New York Infirmary for Women and Children.* (6, 1920)
- Leverton, Ruth M., Ph.D. Department of Home Economics, University of Nebraska, Lincoln. *Associate Professor Human Nutrition Research.* (5, 1942)
- Levin, Louis, Ph.D. Columbia Univ., 630 W. 168th St., New York 32, N. Y. *Research Associate in Biochemistry.* (2, 1939)
- Levine, Harold, Ph.D. Pabst Brewing Co., 917 W. Juneau Ave., Milwaukee, Wis. *Biochemist.* (2, 1933; 5, 1933)
- Levine, Milton, M.S., Ph.D. Inst. of Experimental Medicine, College of Medical Evangelists, 312 N. Boyle Ave., Los Angeles, Calif. (6, 1942)
- Levine, Philip, M.D., M.A. Ortho Research Foundation, Linden, N. J. *Serologist and Bacteriologist.* (6, 1925)
- Levine, Rachmiel, M.D., C.M. Michael Reese Hospital, Chicago, Ill. *Acting Director, Department of Metabolic Research.* (1, 1942)
- Levine, Samuel Z., M.D., New York Hospital, 525 E. 68th St., New York City. *Professor of Pediatrics, Cornell University Medical College; Pediatrician-in-Chief, New York Hospital.* (5, 1933)
- Levine, Victor Emanuel, A.M., Ph.D., M.D. Creighton University School of Medicine, Omaha, Neb. *Professor of Biological Chemistry and Nutrition.* (2, 1936)
- Levinson, Samuel A., M.D. University of Illinois College of Medicine, 808 S. Wood St., Chicago. *Professor of Pathology; Director Laboratories, Research & Educational Hospital.* (4, 1938)
- Levison, Louis A., M.D. 421 Michigan St., Toledo, O. *Physician to Toledo Hospital; Physician to St. Vincent Hospital.* (6, 1916)
- Levy, Milton, Ph.D. 477 First Ave., New York City. *Assistant Professor of Chemistry, New York University College of Medicine.* (2, 1933)
- Levy, Robert L., M.D. 730 Park Ave., New York City. *Professor of Clinical Medicine, College of Physicians and Surgeons, Columbia University.* (3, 1915)
- Lewey, F. H., M.D. University Hospital, University of Pennsylvania, Philadelphia. *Visiting Professor of Neurophysiology and Consultant in Neurology. Major (MC), AUS.* (1, 1937)
- Lewis, Gladys Kinsman, M.A., Ph.D. 401 S. Lafayette St., Denver 9, Colo. (5, 1944)
- Lewis, Howard Bishop, Ph.D. Medical School, University of Michigan, Ann Arbor. *Professor of Biological Chemistry and Director of the College of Pharmacy.* (1, 1925; 2, 1913; 5, 1933)
- Lewis, Julian Herman, M.D. 4750 Champlain Ave., Chicago, Ill. *Associate Professor of Pathology, University of Chicago; Member of the Otto S. A. Sprague Memorial Institute.* (4, 1924)
- Lewis, Robert C., Ph.D. 4200 E. 9th Ave., Denver, Colo. *Professor of Biochemistry, School of Medicine, University of Colorado.* (2, 1931; 5, 1933)
- Lewis, Warren H., M.D. The Wistar Institute of Anatomy and Biology, Woodland Ave. and 36th St., Philadelphia, Pa. *Member; Member of the National Academy of Sciences.* (1, 1919)
- Li, Choh Hao, Ph.D. 4596 Life Science Bldg., University of California, Berkeley. *Assistant Professor of Experimental Biology and Lecturer in Anatomy.* (2, 1944).

- Li, Richard D., M.D.** Peiping Union Medical College, Peiping, China. *Instructor in Pharmacology.* (3, 1941)
- Libby, Raymond L., M.S., Ph.D.** American Cyanamid Co., 1937 W. Main St., Stamford, Conn. *Bio-physicist.* (6, 1938)
- Libet, Benjamin, Ph.D.** Univ. of Chicago, Chicago 37, Ill. *Instructor in Physiology.* (1, 1942)
- Libman, Emanuel, M.D.** 180 E. 64th St., New York City. *Consulting Physician, Mount Sinai Hospital.* (6, 1920)
- Liddell, Howard S., A.M., Ph.D.** Cornell University, Ithaca, N. Y. *Professor of Psychology.* (1, 1925)
- Lieb, Charles C., M.D.** 630 W. 168th St., New York City. *Hosack Professor of Pharmacology, College of Physicians and Surgeons, Columbia University.* (1, 1936; 3, 1915)
- Lieberman, Arnold L., M.D., Ph.D.** 328 No. Country Club Road, Tucson, Ariz. (1, 1934)
- Lifson, Nathan, M.D., Ph.D.\*** 617 Kenwood Parkway, Minneapolis, Minn. *Assistant Professor of Physiology, University of Minnesota Medical School.* (1, 1944)
- Lightbody, Howard D., M.S., Ph.D.** Western Regional Research Laboratory, U. S. Department of Agriculture, Albany 6, Calif. *Principal Biochemist.* (2, 1936)
- Lilienthal, Joseph L., Jr., M.D.\*** School of Aviation Medicine, Naval Air Training Bases, Pensacola, Fla. *Member, Physiological Research Section.* (1, 1945)
- Lillie, Ralph Stayner, Ph.D., Sc.D.** University of Chicago, Chicago, Ill. *Professor Emeritus of General Physiology; Physiologist, Marine Biological Laboratory, Woods Hole, Mass.* (1, 1905; 2, 1913)
- Lillie, R. D., M.D.** Chief Pathology Laboratory, National Institute of Health, Bethesda, Md. *Medical Director, U. S. P. H. S.* (4, 1941)
- Lim, Robert Kho-Seng, Ph.D., D.Sc., F.R.S.E.** Board of Health, Chinese National Government, Chunking, China. (1, 1923)
- Lindsley, Donald B., M.A., Ph.D.** Bradley Home, East Providence, R.I. *Director of Psychological and Neurophysiological Laboratory; Assistant Professor of Psychology, Brown University. Director, N.D.R.C. project, Camp Murphy, Fla.* (1, 1937)
- Linegar, Charles R., Ph.D.** E. R. Squibb and Sons, Biological Laboratory, New Brunswick, N. J. *Chief, Biological Development and Control Laboratory.* (3, 1938)
- Lineweaver, Hans, M.A., Ph.D.** Western Regional Research Laboratory, U. S. Department of Agriculture, Albany 6, Calif. *Senior Biochemist.* (2, 1941)
- Link, Karl Paul, Ph.D.** Biochemistry Building, University of Wisconsin, Madison. *Professor of Biochemistry.* (2, 1931)
- Lintz, William, M.D.** 36 Plaza St., Brooklyn, N. Y. *Late Professor of Immunology and Bacteriology and Clinical Professor of Medicine, Long Island College of Medicine.* (6, 1920)
- Lipman, Mrs. Miriam O., A.M.** Presbyterian Hospital, 620 W. 168th St., New York City. *Research Assistant, Edward Daniels Faulkner Arthritis Clinic.* (6, 1931)
- Lipmann, Fritz, M.D., Ph.D.** Biochemical Research Laboratory, Massachusetts General Hospital, Boston. *Research Chemist; Head, Biochemical Research Laboratory; Research Fellow in Biochemistry and Surgery, Harvard Medical School.* (2, 1941)
- Litchfield, John T., Jr., M.D.** American Cyanamid Co., 1937 W. Main St., Stamford, Conn. *Director of Pharmacology.* (3, 1940)
- Little, James Maxwell, M.S., Ph.D.** Bowman Gray School of Medicine of Wake Forest College, Winston-Salem, N. C. *Assistant Professor of Physiology and Pharmacology.* (1, 1942)
- Livingston, Alfred E., Ph.D.** Temple University School of Medicine, Philadelphia, Pa. *Professor of Pharmacology.* (1, 1917; 3, 1920)
- Lloyd, David P. C., D.Ph.** Rockefeller Inst. for Medical Research, 66th St. and York Ave., New York 21, N. Y. *Associate Member.* (1, 1939)
- Locke, Arthur P., Ph.D.** Zonite Products Corporation, New Brunswick, N. J. *Chief Research Chemist.* (6, 1926)
- Lodholz, Edward, M.D.** Medical Laboratories, University of Pennsylvania, Philadelphia. *Isaac Ott Professor of Physiology, Graduate School of Medicine.* (1, 1913)
- Loeb, Leo, M.D.** Washington University Medical School, St. Louis, Mo. *Professor Emeritus of Pathology; Member, National Academy of Sciences.* (1, 1907; 4, 1913)
- Loebel, Robert O., M.D.** Russell Sage Institute of Pathology, Cornell Medical College, 1300 York Ave., New York City. *Research Fellow; Adjunct Assistant Visiting Physician, Second (Cornell) Medical Division of Bellevue Hospital.* (1, 1928)
- Loew, Earl R., M.S., Ph.D.** Univ. of Ill. College of Med., 1853 W. Polk St., Chicago 12. *Associate Professor of Pharmacology.* (1, 1940)
- Loewe, W. S., M.D.** 17 Cole Terrace, New Rochelle, N. Y. *Hon. Prof. Pharmacology, Hcidelberg; Dept of Pharmacology, Cornell University Medical College.* (3, 1936)
- Logan, Milan A., Ph.D.** University of Cincinnati School of Medicine, Cincinnati, O. *Professor of Biological Chemistry.* (2, 1936)

- Long, C. N. H., M.Sc., D.Sc., M.D. Yale University, New Haven, Conn. *Sterling Professor of Physiological Chemistry.* (1, 1935; 2, 1927)
- Long, Esmond R., M.D. 7th and Lombard Sts., Philadelphia, Pa. *Director, Henry Phipps Institute; Professor of Pathology, University of Pennsylvania.* (4, 1930)
- Long, Perrin Hamilton, M.D. The Johns Hopkins University, 615 N. Wolfe St., Baltimore, Md. *Professor of Preventive Medicine; Colonel, M.C.* (3, 1940)
- Longcope, Warfield T., M.D. Johns Hopkins Hospital, Baltimore, Md. *Professor of Medicine, Johns Hopkins University.* (3, 1921; 4, 1913; 6, 1923)
- Longenecker, Herbert Eugene, M.S., Ph.D. Department of Chemistry, University of Pittsburgh, Pittsburgh, Pa. *Dean of Research in the Natural Sciences and Professor of Biochemistry.* (2, 1940; 5, 1945)
- Looney, Joseph M., M.D. 199th General Hospital, APO #562, c/o Postmaster, New York City. *Lt. Colonel, U. S. A.* (2, 1922)
- Loosli, Clayton Garr, M.D. The University of Chicago, Department of Medicine, Chicago, Ill. *Assistant Professor.* (4, 1940)
- Loosli, J. K., M.S., Ph.D. Animal Nutrition Laboratory, Cornell University, Ithaca, N. Y. *Assoc. Prof. of Animal Nutr. and Assoc. Animal Nutritionist in Exp. Sta.* (5, 1944)
- Lorber, Victor, M.D., Ph.D.\* 1901 East River Terrace, Minneapolis, Minn. *Assistant Professor of Physiology, University of Minnesota Medical School.* (1, 1944)
- Lorente de Nò, Rafael, M.D. The Rockefeller Institute for Medical Research, 66th St. and York Ave., New York City. *Member.* (1, 1937)
- Lorenz, Egon, Ph.D. National Cancer Institute, Bethesda, Md. *Senior Biophysicist.* (4, 1942)
- Loring, H. S., M.S., Ph.D. Stanford University, Calif. *Associate Professor of Biochemistry.* (2, 1938)
- Loveless, Mary H., M.D. New York Hospital, 525 E. 68th St., New York City. *Research Associate, Cornell Medical School; Physician to Out-Patients, New York Hospital.* (6, 1941)
- Lowell, Francis C., M.D. Nine Acre Corner, Concord, Mass. *Instructor in Medicine, Boston City Hospital.* (6, 1942)
- Lowry, Oliver H., M.D., Ph.D. Research Laboratory, Public Health Research Institute of the City of New York, Foot of E. 15th St. *Research Associate.* (2, 1942)
- Lubinski, Herbert, M.D. Jewish General Hospital, 3755 St. Catherine Rd., Montreal, Canada. *Bacteriologist.* (6, 1941)
- Lucas, George H. W., M.A., Ph.D. University of Toronto, Toronto, Canada. *Associate Professor of Pharmacology.* (2, 1925; 3, 1928)
- Luck, James Murray, Ph.D. Stanford University, Stanford, Calif. *Professor of Biochemistry.* (2, 1925)
- Lucké, Balduin, M.D. 141 Montgomery Ave., Bala-Cynwyd, Pa. *Professor of Pathology, University of Pennsylvania Medical School.* (4, 1924)
- Luckhardt, Arno Benedict, M.S., Ph.D., M.D., Sc.D., LL.D. University of Chicago, Chicago, Ill. *Professor of Physiology.* (1, 1911)
- Ludewig, Stephan, Ph.D. University of Virginia School of Medicine, University. *Assistant Professor of Biochemistry.* (2, 1941)
- Luduena, Froilan P., Ph.D., M.D. Department of Pharmacology, Stanford University Medical School, San Francisco, Calif. *Assistant Professor of Pharmacology.* (3, 1941)
- Lukens, Francis D. W., M.D. University of Pennsylvania, 809 Maloney Clinic, 36th and Spruce Sts., Philadelphia. *Assistant Professor of Medicine and Director, George S. Cox Medical Research Institute.* (1, 1938)
- Lund, E. J., Ph.D. Department of Zoology and Physiology, University of Texas, Austin. *Professor of General Physiology.* (1, 1930)
- Lundgren, Harold P., Ph.D. Western Regional Research Laboratory, U.S.D.A., Albany 6, Calif. *Senior Chemist.* (2, 1942)
- Lundy, John Silas, M.D. The Mayo Foundation, Rochester, Minn. *Chief of Section on Anesthesia.* (3, 1935)
- Lurie, Max B., M.D. Henry Phipps Institute, 7th and Lombard Sts., Philadelphia, Pa. *Associate Professor of Experimental Pathology.* (4, 1934; 6, 1930)
- Lutz, Brenton R., Ph.D. Boston University, 688 Boylston St., Boston, Mass. *Professor of Biology.* (1, 1925)
- Luyet, Basile J., Sc.D. (Biol.), Sc.D. (Physics). St. Louis University School of Medicine, St. Louis, Mo. *Professor of Biology.* (1, 1936)
- Lyall, Harold W., A.M., Ph.D. Division of Laboratories and Research, New York State Department of Health, Albany. *Assistant Director in charge of Antitoxin, Serum, and Vaccine Laboratories.* (6, 1937)
- Lyman, Carl M., Ph.D. Division of Swine Husbandry, Agricultural Experiment Station, College Station, Texas. *Nutritionist.* (2, 1940)
- Lyman, John F., Ph.D. Townshend Hall, Ohio State University, Columbus. *Professor of Agricultural Chemistry.* (2, 1920; 5, 1933)
- Maaske, Clarence A., Ph.D.\* Mayville, Wis. *Project Engineer, Physiology Branch.* (1, 1945)
- Macallum, A. Bruce, M.D., Ph.D. Medical School, University of Western Ontario, London, Ont., Canada. *Professor of Biochemistry.* (2, 1914)

- MacArthur, Edith H., A.M., Ph.D. Skidmore College, Saratoga Springs, N. Y. Professor and Director of Home Economics. (5, 1933)
- MacCorquodale, D. W., M.S., Ph.D. Abbott Laboratories, North Chicago, Ill. Head, Biochemical Research. (2, 1934)
- MacFadyen, Douglas A., M.A., M.D. Alfred I. DuPont Institute of the Nemours Foundation, Wilmington, Del. Chief of Biochemistry (On leave to U. S. Army, Captain). (2, 1942)
- MacKay, Eaton M., M.D. The Scripps Metabolic Clinic, La Jolla, Calif. (1, 1930)
- Mackenzie, Cosmo G., D.Sc. Plant Park, Tampa, Fla. (5, 1942)
- Mackenzie, George M., M.D. Mary Imogene Bassett Hospital, Cooperstown, N. Y. Physician-in-Chief; Director, Otsego County Laboratories. (6, 1921)
- MacLeod, Colin M., M.D. New York University College of Medicine, 477 First Ave., New York City. Professor of Bacteriology. (6, 1937)
- MacLeod, Florence L., M.A., Ph.D. University of Tennessee, Knoxville. Professor of Nutrition. (2, 1927; 5, 1933)
- MacLeod, Graee, M.A., Ph.D. 106 Morningside Drive, New York City. Professor Emeritus of Nutrition, Teachers College, Columbia University. (2, 1924; 5, 1933)
- MacLeod, John, M.S., Ph.D. Cornell University Medical College, 1300 York Ave., New York City. Research Associate of Anatomy. (1, 1942)
- MaeNabb, Andrew L., V.S., B.V.Sc., F.A.P.H.A. Department of Health of Ontario, Toronto, Canada. Director of Laboratories. (6, 1941)
- MacNeal, Ward J., M.D. New York Post-Graduate Medical School and Hospital, 303 E. 20th St., New York City. Professor of Bacteriology. (4, 1925)
- MaeNider, William deB., M.D., Sc.D., LL.D. University of North Carolina, Chapel Hill. Kenan Research Professor of Pharmacology; Member, National Academy of Sciences. (1, 1912; 2, 1912; 3, 1909; 4, prior to 1920)
- Macht, David Israel, M.D., Phar. D. (Hon.), Litt. D. 3420 Auchentoroly Ter., Baltimore, Md. Research Pharmacologist, Sinai Hospital Laboratories, and Consultant Pharmacologist, Sinai Hospital. (1, 1916)
- MacPhillamy, Betty Bowser, M.S., Ph.D. 35 Beekman Rd., Summit, N. J. Virologist. (6, 1944)
- Madden, Sidney C., M.D. Emory University, School of Medicine, Atlanta, Ga. Professor of Pathology. (4, 1939)
- Maddock, Stephen, M.D. Boston City Hospital, Boston, Mass. Director of Surgical Research Laboratory. (4, 1931)
- Madsen, Louis L., Ph.D. Dept. of Animal Husbandry, Utah State Agricultural College, Logan. Nutritionist. (5, 1940)
- Maes, Julian P., M.D.\* Dartmouth Medical School, Hanover, N. H. Department of Pharmacology. (1, 1943)
- Magath, Thomas B., M.S., Ph.D., M.D. Mayo Clinic, Rochester, Minn. Associate Professor of Clinical Bacteriology and Parasitology, University of Minnesota, Mayo Foundation; Consultant Physician in Clinical Laboratories, Mayo Clinic. (1, 1928)
- Magill, Thomas P., M.D. Cornell University Medical College, 1300 York Ave., New York City. (6, 1937)
- Magoun, Horace W., Ph.D. Northwestern University Medical School, 303 E. Chicago Ave., Chicago, Ill. Professor of Microscopic Anatomy. (1, 1937)
- Mahon, Eleanor Conway, Ph.D. Iron River, Mich. (4, 1940)
- Main, Rolland J., Ph.D. Medical College of Virginia, Richmond. Professor of Physiology. (1, 1936)
- Maison, George L., M.S., M.D. Aero-Medical Research Laboratory, Engineering Division, Wright Field, Dayton, O. 1st Lt., Medical Corps., Assistant Professor of Physiology, Wayne University, Detroit, Mich. (1, 1939)
- Major, Randolph T., M.Sc., Ph.D. Coles Ave., Mountainside, Westfield, N. J. Director of Research, Merck & Co., Inc., Rahway, N. J. (2, 1942)
- Mallory, G. Kenneth, M.D. Mallory Institute of Pathology, Boston City Hospital, Boston, Mass. Professor. (4, 1940)
- Mallory, Tracy B., M.D. Massachusetts General Hospital, Boston. Director of Pathology and Bacteriology; Assistant Professor of Pathology, Harvard Medical School. (4, 1937)
- Maloney, Arnold H., Ph.D., M.D., LL.D. Howard University School of Medicine, Washington, D. C. Professor and Head of Department of Pharmacology. (3, 1932)
- Maltaner, Frank, Ph.D. 388 New Scotland Ave., Albany, N. Y. Associate Biochemist, Division of Laboratories and Research, New York State Department of Health. (6, 1920)
- Maluf, N. S. Rustum, M.S., Ph.D. Company D, SCSU, No. 1144, 427 Vanderbilt Hall, Harvard School, Boston, Mass. (1, 1942)
- Man, Evelyn B., Ph.D. 333 Cedar St., New Haven, Conn. Assistant Professor in the Biochemistry Laboratory, Dept. of Psychiatry, Yale University School of Medicine. (2, 1936)
- Manery, Jeanne Forest, M.A., Ph.D. Medical School, University of Toronto, Toronto, Ont., Canada. Demonstrator in Biochemistry. (1, 1937)

- Mann, Frank C., M.A., M.D., Sc.D., LL.D. Mayo Clinic, Box 256, Rochester, Minn. *Director, Division of Experimental Medicine; Professor of Experimental Medicine, Mayo Foundation.* (1, 1916; 3, 1923; 4, 1924)
- Manning, G. W., M.D.\* 20 Woodington Ave., Toronto, Ontario, Canada. *Medical Officer in Charge, No. 2 R.C.A.F. Research Unit.* (1, 1944)
- Manville, Ira Albert, M.A., M.D., Ph.D. 811 N. W. 19th Ave., Portland 9, Ore. (1, 1933)
- Manwaring, Wilfred H., M.D. Stanford University, Palo Alto, Calif. *Professor Emeritus of Bacteriology and Experimental Pathology.* (4, prior to 1920; 6, 1917)
- Marine, David, A.M., M.D. 18 Baltimore Ave., Rehoboth, Del. (1, 1910; 4, 1913)
- Markee, Joseph E., Ph.D.\* Duke University School of Medicine, Durham, N. C. *Professor of Anatomy.* (1, 1945)
- Markowitz, J., M.D., Ph.D. 220 Bloor St., Toronto, Ont., Canada. *Research Associate in Physiology, University of Toronto, Faculty of Medicine.* (1, 1929)
- Marmont, George H., Ph.D. 4855 Fourth Ave., Detroit, Mich. *Electronic Engineer, Bendix Aviation Research Laboratories.* (1, 1941)
- Marmorston, Jessie. 415 N. Camden Drive, Beverly Hills, Calif. (6, 1932)
- Marrazzi, Amedeo S., M.D. Wayne University College of Medicine, Detroit 26, Mich. *Professor and Head of the Department of Pharmacology.* (3, 1938)
- Marsh, Gordon, Ph.D.\* State University of Iowa, Iowa City. *Assistant Professor of Zoology.* (1, 1944)
- Marsh, M. Elizabeth, M.S., Ph.D. Killian Research Laboratories, 49 W. 45th St., New York City. *Assistant Director.* (1, 1929; 5, 1933)
- Marshak, Alfred George, M.A., Ph.D. Radiation Laboratory, University of California, Berkeley. *Research Associate and Finney-Howell Fellow.* (1, 1940)
- Marshall, Eli Kennerly, Jr., Ph.D., M.D., LL.D. Johns Hopkins Medical School, Baltimore, Md. *Professor of Pharmacology and Experimental Therapeutics; Member, National Academy of Sciences.* (1, 1915; 2, 1913; 3, 1915)
- Marshall, Wade H., Ph.D. 9700 Brunett Ave., Silver Spring, Md. Wilmer Ophthalmological Institute, Johns Hopkins Hospital Baltimore, Md. *Associate in Physiological Optics, Johns Hopkins Hospital.* (1, 1937)
- Martin, Arthur W., Jr., Ph.D.\* 202 Physiology Hall, University of Washington, Seattle. *Associate Professor of Animal Biology.* (1, 1944)
- Martin, Donald S., M.D. Duke Hospital, Durham, N. C. *Associate Professor of Bacteriology and Associate in Medicine, Duke University School of Medicine.* (4, 1940; 6, 1943)
- Martin, Stevens J., M.A., Ph.D. Tilton General Hospital, Fort Dix, N. J. *Capt. M. C., Chief of Sections on Anesthesia and Operating Pavilion, and Resuscitation and Oxygen Therapy.* (1, 1933)
- Mason, Edward C., M.D., Ph.D. University of Oklahoma School of Medicine, Oklahoma City. *Professor of Physiology.* (1, 1935)
- Mason, H. L., M.A., Ph.D. Mayo Clinic, Rochester, Minn. *Associate Professor of Physiological Chemistry, The Mayo Foundation, University of Minnesota.* (2, 1941)
- Mason, Karl Ernest, Ph.D. The University of Rochester, School of Medicine and Dentistry, Rochester, N. Y. *Professor of Anatomy.* (1, 1932; 5, 1941)
- Mason, Morton F., Ph.D. Parkland Hospital, Oak Lawn Ave., Dallas, Texas. *Professor of Pathological Chemistry and Experimental Medicine, Southwestern Medical College.* (2, 1938)
- Massengale, Oliver N., Ph.D. Mead Johnson & Co., Research Laboratory, Evansville, Ind. *Research Biochemist.* (2, 1937)
- Masson, Georges M. C., Ph.D.\* McGill University, Montreal, Canada. *Research Associate.* (1, 1944)
- Mast, S. O., Ph.D. Johns Hopkins University, Baltimore, Md. *Professor of Zoology.* (1, 1920)
- Mathews, Albert Prescott, Ph.D., D.Sc. (hon.). Woods Hole, Mass. *Professor Emeritus of Biochemistry, Univ. of Cincinnati.* (1, 1898; 2, 1906)
- Mattill, Henry A., A.M., Ph.D. State University of Iowa, Iowa City. *Professor of Biochemistry.* (1, 1913; 2, 1909; 5, 1933)
- Maurer, Frank W., Ph.D. 301 Lake Ave., Newton Highlands 61, Mass. (1, 1941)
- Mautz, Frederick R., M.D.\* Western Reserve School of Medicine, Cleveland 6, O. *Assistant Professor of Surgery.* (1, 1945)
- Mavor, James Watt, Ph.D. Union College, Schenectady, N. Y. *Professor of Biology.* (1, 1930)
- Mayerson, Hymen S., Ph.D. Tulane University School of Medicine, Station 20, New Orleans, La. *Associate Professor of Physiology.* (1, 1928)
- Maynard, Leonard A., Ph.D., Sc.D. Cornell University, Ithaca, N. Y. *Professor of Nutrition; Director, School of Nutrition; Member National Academy of Sciences.* (2, 1930; 5, 1933)
- Mazur, Abraham, M.A., Ph.D. Medical Research Laboratory, Edgewood Arsenal, Md. *Captain, Sanitary Corps, U. S. Army; Instructor, Department of Chemistry, City College of New York (on leave).* (2, 1944)

- McCann, William S., M.D., D.Sc. (Hon.)** USS Refuge AH-11, Fleet P.O., New York. *Captain (MC) USNR. The Charles A. Dewey Professor of Medicine, University of Rochester, School of Medicine.* (On leave.) (2, 1923; 5, 1933)
- McCarrell, June D.** Dept. of Physiology, Vassar College, Poughkeepsie, N. Y. (1, 1942)
- McCawley, Elton Leeman, Ph.D.** Yale Medical School, New Haven, Conn. *Instructor in Pharmacology.* (3, 1944)
- McCay, Clive M., M.S., Ph.D.** Naval Medical Research Institute, Bethesda, Md. *Lt. Commander in Charge of Research in Nutrition.* (2, 1929; 5, 1933)
- McChesney, Evan William, Ph.D.\*** Winthrop Chemical Co., 33 Riverside Ave. Rensselaer, N. Y. *Research Biochemist.* (1, 1944)
- McClellan, Walter S., M.D.** Saratoga Spa, Saratoga Springs, N. Y. *Medical Director; Associate Professor of Medicine, Albany Medical College.* (1, 1931)
- McClendon, J. F., M.S., Ph.D.** Route 1, Box 383, Trooper Road, Norristown, Pa. *Research Professor of Physiology, Hahnemann Medical College.* (1, 1910; 2, 1914; 5, 1935)
- McClosky, William T., B.A.** 5120 7th St., N.W., Washington, D. C. *Senior Pharmacologist, Div. of Pharmacology, Food and Drug Administration.* (3, 1929)
- McCollum, Elmer Verner, M.A., Ph.D., Sc.D., LL.D.** Johns Hopkins University, School of Hygiene and Public Health, 615 N. Wolfe St., Baltimore, Md. *Professor of Biochemistry; Member, National Academy of Sciences.* (2, 1910; 5, 1933)
- McCouch, Grayson Prevost, M.D.** University of Pennsylvania, Philadelphia. *Assistant Professor of Physiology.* (1, 1925)
- McCrea, Forrest D., Ph.D.** Duke University School of Medicine, Durham, N. C. *Associate Professor of Physiology and Pharmacology.* (1, 1929; 3, 1937)
- McCradden, F. H., M.D.** 501 Boylston St., Boston, Mass. *Assistant Medical Director, New England Mutual Life Insurance Co.* (2, 1906)
- McCullagh, D. Roy, M.Sc. (Man.); Ph.D. (Cantab.), F.I.C.** 150 Northfield Rd., Bedford, O. *Vice-President.* (2, 1932)
- McCulloch, Warren Sturgis, M.A., M.D.** University of Illinois, College of Medicine, 912 S. Wood St., Chicago. *Associate Professor of Psychiatry.* (1, 1936)
- McCutcheon, Morton, M.D.** University of Pennsylvania Medical School, Philadelphia. *Professor of Pathology.* (4, 1925)
- McDonald, Francis Guy, M.S., Ph.D.** Research Laboratory, Mead Johnson & Co., Evansville, Ind. *Research Biochemist.* (2, 1936)
- McElroy, L. W.** Dept. of Animal Science, University of Alberta, Edmonton, Canada. *Assistant Prof. of Animal Husbandry.* (5, 1944)
- McElroy, William D., Ph.D.\*** NRC Fellow at Dept. of Biology, Stanford University, Calif. (1, 1945)
- McEllroy, William Swindler, M.D.** School of Medicine, University of Pittsburgh, Pittsburgh, Pa. *Professor of Physiological Chemistry; Dean, School of Medicine.* (2, 1919)
- McFarland, Ross A.,\* Ph.D.** Harvard University, Division of Industrial Research, Graduate School of Business Administration, Soldiers Field, Boston, Mass. *Assistant Professor of Industrial Research.* (1, 1943)
- McFarlane, William Douglas, Ph.D.** Macdonald College, (McGill University), Macdonald College, P. Q., Canada. *Professor of Chemistry.* (2, 1933)
- McGinty, Daniel A., M.A., Ph.D.** Parke, Davis & Co., Detroit, Mich. *Research Physiologist.* (1, 1925)
- McGuigan, Hugh Alister, Ph.D., M.D.** 1853 W. Polk St., Chicago, Ill. *Professor of Pharmacology and Therapeutics, College of Medicine, University of Illinois.* (1, 1907; 2, 1906; 3, 1913)
- McHargue, J. S., M.S., Ph.D., D.Sc.** Department of Chemistry, Kentucky Agricultural Experiment Station, University of Kentucky, Lexington. *Emeritus Member.* (2, 1927)
- McHenry, E. W., M.A., Ph.D., F.R.S.C.** School of Hygiene, University of Toronto, Toronto, Canada. *Assistant Director, Connaught Laboratories; Associate Professor in Charge of Nutrition.* (2, 1938; 5, 1935)
- McIntyre, A. R., Ph.D., M.D.** College of Medicine, University of Nebraska, 42nd and Dewey Ave., Omaha. *Professor of Physiology and Pharmacology.* (1, 1933; 3, 1938)
- McKee, Clara M.** Squibb Institute for Medical Research, New Brunswick, N. J. *Assistant in Microbiology.* (6, 1941)
- McLain, Paul L., M.D.** University of Pittsburgh Medical School, Pittsburgh, Pa. *Assistant Professor of Physiology and Pharmacology; Major, M.C.* (3, 1940)
- McLean, Franklin C., Ph.D., M.D.** University of Chicago, Chicago, Ill. *Professor of Pathological Physiology.* (1, 1914; 2, 1916; 3, 1916)
- McLester, James S., M.D., LL.D.** University of Alabama, 930 S. 20th St., Birmingham. *Professor of Medicine.* (5, 1933)
- McMaster, Philip D., M.D.** The Rockefeller Institute for Medical Research, 66th St. and York Ave., New York City. (4, 1924)
- McMeekin, Thomas L., Ph.D.** Eastern Regional Research Laboratory, U. S. Department of

- Agriculture, Philadelphia, Pa. *Senior Chemist.* (2, 1935)
- McNaught, James Bernard, M.D. University of Colorado School of Medicine, Denver 7. *Professor of Pathology.* (4, 1930)
- McPhail, Murchie Kilburn, Ph.D. Vick Chemical Co., Research Labs., 35-22 Linden Place, Flushing, N. Y. (3, 1941)
- McQuarrie, Irvine, Ph.D., M.D. University of Minnesota, Minneapolis. *Professor and Head of Department of Pediatrics.* (4, 1927; 5, 1933)
- Medes, Grace, Ph.D. Lankenau Hospital Research Institute, Philadelphia, Pa. *Research Physiological Chemist.* (2, 1930)
- Medlar, Edgar M., M.D. Path. Bldg., Room 708 Bellevue Hospital, 1st Ave. at 26th St., New York, N. Y. *Pathologist.* (4, 1927)
- Meck, Walter J., Ph.D. University of Wisconsin, Madison. *Professor of Physiology; Assistant Dean of the Medical School.* (1, 1908)
- Mellon, Ralph R., M.D., M.Sc., Dr. P.H., Sc.D. (hon.). Institute of Pathology, Western Pennsylvania Hospital, Pittsburgh. *Director.* (6, 1918)
- Melnick, Daniel, Ph.D. Food Research Laboratories, Inc., 48-14 33rd St., Long Island City, N. Y. *Chief Chemist.* (2, 1940; 5, 1942)
- Melville, Kenneth Ivan, M.Sc., M.D., C.M. McGill University, Montreal, Canada. *Assistant Professor of Pharmacology.* (3, 1931)
- Mendenhall, Walter L., S.M., M.D. Boston University Medical School, 80 E. Concord St., Boston, Mass. *Professor of Pharmacology.* (1, 1915; 3, 1917)
- Mendez, Rafael, M.D. Loyola University School of Medicine, 706 S. Wolcott Ave., Chicago, Ill. *Assistant Professor of Pharmacology.* (3, 1944)
- Menkin, Valy, M.A., M.D. Dept. of Pathology, Duke University School of Medicine, Durham, N. C. *Assistant Professor of Pathology.* (1, 1932; 4, 1932; 6, 1931)
- Menten, Maud L., M.D., Ph.D. University of Pittsburgh, Pittsburgh, Pa. *Associate Professor of Pathology.* (1, 1915; 4, 1927)
- Mettier, Stacy R., M.D. University of California Hospital, San Francisco. *Associate Professor of Medicine.* (4, 1932)
- Mettler, Fred A., A.M., Ph.D., M.D. Department of Neurology, College of Physicians and Surgeons, Columbia University, New York City. *Associate Professor of Anatomy.* (1, 1937)
- Meyer, Curtis E., M.S., Ph.D. The Upjohn Co., Kalamazoo, Mich. *Research Chemist.* (2, 1942)
- Meyer, Karl, M.D., Ph.D. 630 W. 168th St., New York City. *Associate Professor of Biochemistry, Dept. of Ophthalmology, College of Physicians and Surgeons, Columbia University.* (2, 1934)
- Meyer, Karl F., M.D., Ph.D. Medical Center, San Francisco, Calif. *Professor of Bacteriology, University of California. Director of the George Williams Hooper Foundation for Medical Research.* (4, 1930; 6, 1922)
- Meyerhof, Otto, M.D., LL.D. Department of Physiological Chemistry, University of Pennsylvania School of Medicine, Philadelphia. *Research Professor of Biochemistry.* (2, 1941)
- Michaelis, Leonor, M.D. Rockefeller Institute for Medical Research, 66th St. and York Ave., New York City. *Member Emeritus.* (2, 1929)
- Mickelsen, Olaf, Ph.D. University of Minnesota, Department of Physiological Hygiene, Stadium South Tower, Minneapolis. *Assistant Professor.* (2, 1944)
- Mider, George Burroughs, M.D. Strong Memorial Hospital, Rochester 7, N. Y. (4, 1940)
- Miles, Walter R., A.M., Ph.D. 333 Cedar St., New Haven, Conn. *Professor of Psychology, The School of Medicine and the Institute of Human Relations, Yale University; Member of the National Academy of Sciences.* (1, 1919)
- Milhorat, Ade T., M.D. Cornell University Medical College, 1300 York Ave., New York City. *Assistant Professor of Medicine and Instructor in Pharmacology; Research Fellow, Russell Sage Institute of Pathology.* (1, 1934; 3, 1937; 5, 1935)
- Miller, Augustus Taylor, Jr., Ph.D.\* University of North Carolina Medical School, Chapel Hill. *Associate Professor of Physiology.* (1, 1944)
- Miller, Benjamin F., Ch.E., M.D. 60 Gramercy Park North, New York 10, N. Y. *Major (Surgeon, R), U. S. Public Health Service. Assistant Professor of Medicine, University of Chicago (On leave for duration).* (2, 1938)
- Miller, Carey D., M.S. University of Hawaii, Honolulu. *Professor of Food and Nutrition, Hawaii Agricultural Experimental Station.* (5, 1942)
- Miller, C. Phillip, M.D., M.S. University of Chicago, Chicago, Ill. *Professor of Medicine.* (4, 1925; 6, 1928)
- Miller, Edgar C. L., M.D. % Library, Medical College of Virginia, Richmond. *Directing Librarian.* (6, 1913)
- Miller, Edgar G., Jr., Ph.D. 630 W. 168th St., New York City. *Professor of Biological Chemistry, Columbia University.* (2, 1930)
- Miller, Franklin R., M.D. Jefferson Medical College and Hospital, Division of Hematology, Philadelphia, Pa. *Associate Professor of Medicine.* (4, 1940)
- Miller, Frederick R., A.M., M.D., F.R.C.P. (C), F.R.S. Faculty of Medicine, University of Western Ontario, London, Ont., Canada. *Professor of Physiology.* (1, 1908)

- Miller, G. H., A.M., M.D. American University of Beirut, Beirut, Syria. *Dean of the College of Medicine.* (3, 1925)
- Miller, Lloyd C., Ph.D. Research and Biologic Laboratory, Winthrop Chemical Co., Rensselaer, N. Y. *Senior Pharmacologist.* (3, 1938)
- Miller, R. C., Ph.D. Pennsylvania State College, State College. *Assistant Professor Agricultural and Biological Chemistry.* (5, 1935)
- Miller, Zelma Baker, Ph.D., Naval Medical Research Institute, National Naval Medical Center, Bethesda, Md. *Biochemist.* (2, 1940)
- Millikan, Glenn A., Ph.D. Johnson Foundation, University of Pennsylvania, Philadelphia. *Fellow in Biophysics.* (1, 1940)
- Mills, Clarence A., Ph.D., M.D. 228 Woolper Ave., Cincinnati, O. *Professor of Experimental Medicine, University of Cincinnati.* (1, 1921; 2, 1921)
- Minot, Annie Stone, Ph.D. Vanderbilt University Medical School, Nashville, Tenn. *Research Associate, Department of Pharmacology.* (1, 1923)
- Mirsky, Alfred E., Ph.D. The Jewish Hospital, Cincinnati 29, O. (2, 1941)
- Mirsky, I. Arthur, M.Sc., M.D., C.M. The Jewish Hospital, Cincinnati, O. *Director, The May Institute for Medical Research; Assistant Professor of Biochemistry, University of Cincinnati.* (1, 1936)
- Mitchell, Harold H., M.S., Ph.D. Dept. of Bacteriology, Washington University Medical School, St. Louis, Mo. *Research Fellow.* (6, 1943)
- Mitchell, Harold H., M.S. 4833 Fountain Ave., Los Angeles, Calif. (2, 1919; 5, 1933; 6, 1943)
- Mitchell, Helen S., Ph.D. 699 Forest Rd., New Haven 15, Conn. *Nutrition Director, American Red Cross, New Haven Chapter.* (2, 1925; 5, 1933)
- Mitchell, Philip H., Ph.D. Brown University Providence 12, R. I. *Robert P. Brown Professor of Biology.* (2, 1909)
- Modell, Walter, M.D. Cornell University Medical College, 1300 York Ave., New York, N. Y. *Instructor in Pharmacology.* (3, 1944)
- Moe, Gordon Kenneth, Ph.D., M.D. University of Michigan, Ann Arbor. *Assistant Professor of Pharmacology.* (3, 1944)
- Molitor, Hans, M.D. 50 Lawrence St., Rahway, N. J. *Director, Merck Institute for Therapeutic Research.* (1, 1933; 3, 1942)
- Molomut, Norman, M.A., Ph.D. 200 Walnut St., Yellow Springs, O. *Assistant Bacteriologist, Department of Medicine, Columbia University (on leave); First Lieutenant, Army of U. S. Aero Medical Research.* (6, 1942)
- Moon, Virgil H., M.Sc., M.D. Jefferson Medical College, Philadelphia, Pa. *Professor of Pathology.* (4, 1934)
- Moore, A. R., Ph.D. University of Oregon, Eugene. *Research Professor of General Physiology in the Department of Psychology.* (1, 1912)
- Moore, Carl Vernon, M.D. Washington University School of Medicine, St. Louis, Mo. *Associate Professor of Medicine.* (4, 1938; 5, 1941)
- Moore, Lane A., Ph.D. University of Maryland, College Park. *Research Assistant in Dairy Husbandry.* (5, 1940)
- Moore, Robert A., M.D. Washington University Medical School, St. Louis, Mo. *Professor of Pathology.* (4, 1929)
- Moore, Robert M., M.D. 5808 Westminster, St. Louis, Mo. *Lt. Col., M.C.* (1, 1932)
- Moorhouse, Victor Henry K., M.B. University of Manitoba, Winnipeg, Canada. *Professor of Physiology.* (1, 1912)
- Morgan, Agnes Fay, M.S., Ph.D. University of California, Berkeley. *Professor of Home Economics; Biochemist, Agric. Exp. Station; Head, Department of Home Economics.* (2, 1929; 5, 1933)
- Morgan, Clifford T., M.A., Ph.D.\* Harvard University, Cambridge, Mass. *Faculty Instructor in Physiological Psychology.* (1, 1943)
- Morgulis, Sergius, A.M., Ph.D. University of Nebraska College of Medicine, Omaha. *Professor of Biochemistry.* (1, 1914; 2, 1916)
- Morison, Robert S., M.D. Rockefeller Foundation, 66th St. and York Ave., New York City. *Assist. Director of the Med. Sciences.* (1, 1938)
- Moritz, Alan R., M.D. Harvard Medical School, Boston, Mass. *Professor of Legal Medicine.* (4, 1934)
- Morrell, Clarence Allison, M.A., Ph.D. Department of Pensions and National Health, Laboratory of Hygiene, Sussex and John Sts., Ottawa, Canada. *Senior Pharmacologist.* (3, 1937)
- Morris, Harold P., M.S., Ph.D. National Cancer Institute, Bethesda, Md. *Senior Nutrition Chemist, U. S. Public Health Service.* (2, 1944; 5, 1943)
- Morris, Marion C. Public Health Research Institute of City of New York, Foot of East 15th St., New York City. (6, 1936)
- Morrison, Dempsey B., M.S., Ph.D. University of Tennessee College of Medicine, Memphis. *Associate Professor of Chemistry.* (2, 1936)
- Morrison, James L., Ph.D. Emory University School of Medicine, Emory University, Ga. *Assistant Professor of Pharmacology.* (3, 1944)
- Morse, Minerva, M.S., Ph.D. 5525 Kimball Ave., Chicago, Ill. *Research Associate, Department of Pediatrics, University of Chicago.* (2, 1934)

- Morse, Withrow, Ph.D. 32 Manchester Rd., Eastchester, via Tuckahoe, N. Y. *Consultant.* (2, 1914)
- Mortimer, Bernard, Ph.D., M.D. 250 N. Ottawa St., Joliet, Ill. Cook County Hospital, Chicago, Ill. (1, 1936)
- Morton, John J., M.D. University of Rochester, School of Medicine and Dentistry, Rochester, N. Y. *Professor of Surgery.* (4, 1927)
- Mosenthal, Herman O., M.D. 889 Lexington Ave., New York City. *Professor of Medicine, New York Post-Graduate Medical School.* (2, 1915)
- Moulton, C. Robert, Ph.D. 5712 S. Kenwood Ave., Chicago, Ill. *Editor.* (5, 1933)
- Moxon, Alvin L., M.S., Ph.D. College Station, Brookings, S. D. *Chemist, South Dakota Agricultural Experiment Station.* (2, 1944)
- Moyer, Carl A., Ph.D.\* Seymour Hospital, Eloise, Mich. *Assistant Professor of Surgery.* (1, 1943)
- Mudd, Stuart, M.A., M.D. University of Pennsylvania, Philadelphia. *Professor of Bacteriology.* (1, 1921; 4, 1927; 6, 1927)
- Muehlberger, Clarence W., M.S., Ph.D. State Health Department Laboratories, Lansing, Mich. *State Toxicologist.* (3, 1928)
- Mueller, J. Howard, M.S., Ph.D. 2176 Centre St., N. Roxbury, Mass. *Professor of Bacteriology and Immunology, Harvard Medical School.* (2, 1922; 4, 1927; 6, 1920)
- Mukherji, B., M.B., D.Sc. All-India Institute of Hygiene and Public Health, Calcutta. *Director, Biochemical Standardization Laboratory.* (3, 1938)
- Mulder, Arthur G., Ph.D. University of Tennessee College of Medicine, Memphis. *Associate Professor of Physiology.* (1, 1937)
- Mulinos, M. G., M.D., Ph.D. New York Medical College, Flower and Fifth Avenue Hospitals, Fifth Ave. and 105th St., New York 29, N. Y. *Associate Professor of Pharmacology.* (3, 1931)
- Mull, James W., Ph.D. Maternity Hospital, 2065 Adelbert Rd., Cleveland, O. *Senior Instructor in Biochemistry in charge of Biochemical Research in Obstetrics, Western Reserve University.* (2, 1937)
- Mullin, F. J., M.S., Ph.D. University of Chicago, Chicago, Ill. *Assistant Professor of Physiology.* (1, 1937)
- Munsell, Hazel E. 8 N. Main St., Monson, Mass. (5, 1933)
- Muntwyler, Edward, Ph.D. Long Island College of Medicine, 350 Henry St., Brooklyn, N. Y. *Professor of Biochemistry.* (2, 1931)
- Murlin, John R., A.M., Ph.D., Sc.D. University of Rochester Medical School, 260 Crittenden Blvd., Rochester, N. Y. *Professor Emeritus of Physiology and Director of Department of Vital Economics.* (1, 1906; 2, 1908; 5, 1933)
- Murphy, James B., M.D. Rockefeller Institute for Medical Research, 66th St. and York Ave., New York City. *Member.* (4, prior to 1920)
- Murray, Everitt G. D., O.B.E., B.A. honors in Natural Science, M.A., L.M.S.S.A., F.R.S.C. McGill University, Montreal, Canada. *Professor of Bacteriology and Immunology and Head of the Department, McGill University; Bacteriologist-in-Chief to the Royal Victoria Hospital, to the Children's Memorial Hospital and to the Alexandra Hospital.* (6, 1933)
- Myers, Chester N., Ph.D., Sc.D. 34 Cedar Place, Yonkers 5, N. Y. *Chief, Division Chemotherapy, N. Y. Skin and Cancer Hospital; Associate in Dermatology and Syphilology, College of Physicians and Surgeons; Research Chemist, Vanderbilt Clinic; Director, Chemical and Clinical Research, H. A. Metz Laboratories, Inc.* (2, 1922)
- Myers, Victor C., M.A., Ph.D., Sc.D. School of Medicine, Western Reserve University, Cleveland, O. *Professor and Director of Biochemistry.* (1, 1916; 2, 1910; 5, 1933)
- Nachmansohn, David, M.D. Dept. of Neurology, College of Physicians and Surgeons, Columbia University, 630 W. 168th St., New York City. *Research Associate in Neurology.* (1, 1940)
- Nadler, J. Ernest, M.D., Med. D.Sc. U. S. Navy Recruiting Station, 383 Madison Ave., New York, N. Y. *Instructor in Medicine; Lt. Comdr. (M.C.)* (3, 1940)
- Nahum, Louis N., M.D. 1142 Chapel St., New Haven, Conn. *Assistant Professor of Physiology, Yale University.* (1, 1934)
- Nash, Thomas P., Jr., M.A., Ph.D. 875 Monroe Ave., Memphis, Tenn. *Professor of Chemistry, College of Medicine; Dean of School of Biological Sciences, University of Tennessee.* (2, 1923)
- Nasset, Edmund S., M.S., Ph.D. University of Rochester, 260 Crittenden Blvd., Rochester, N. Y. *Associate Professor of Physiology.* (1, 1932; 5, 1940)
- Nathanson, Ira T., M.S., M.D.\* Massachusetts General Hospital, Boston. *Instructor in Surgery, Harvard Medical School; Assistant in Surgery, Mass. General Hospital.* (1, 1943)
- Nathanson, Morris D., M.D. 658 S. Bonnie Brae St., Los Angeles, Calif. *Associate Clinical Professor of Medicine, University of Southern California School of Medicine.* (3, 1940)
- Necheles, Heinrich, M.D., Ph.D. Michael Reese Hospital, Chicago, Ill. *Director, Dept. of Gastro-intestinal Physiology, Michael Reese Hospital; Professorial Lecturer in Physiology, University of Chicago.* (1, 1929)

- Neill, James M., Ph.D. Medical College, Cornell University, 1300 York Ave., New York City. *Professor of Bacteriology and Immunology.* (6, 1930)
- Neilson, Charles Hugh, A.M., Ph.D., M.D. Humboldt Building, St. Louis, Mo. *Associate Dean and Professor of Medicine, St. Louis University Medical School.* (2, 1906)
- Nelson, Arthur A., M.D., Ph.D. Food and Drug Administration, Federal Security Agency, Washington, D. C. *Senior Pathologist, Division of Pharmacology.* (4, 1942)
- Nelson, Carl Ferdinand, M.D., Ph.D. Department of Biochemistry, University of Kansas, Lawrence. *Professor of Physiological Chemistry.* (2, 1914)
- Nelson, Carl T., A.M., D.M.D., M.D. 4th Service Command Laboratory, Ft. McPherson, Ga. *Captain, M.C., A. U. S.* (6, 1943)
- Nelson, Erwin E., Ph.D., M.D. The Wellcome Research Laboratories, Tuckahoe, N.Y. *Director.* (1, 1923; 3, 1924)
- Nelson, E. M., M.S., Ph.D. Food and Drug Administration, Federal Security Agency, Washington 25, D. C. *Chief, Vitamin Division.* (2, 1927; 5, 1933)
- Nelson, John B., Ph.D. Rockefeller Institute for Medical Research, Princeton, N. J. *Associate Member.* (4, 1934)
- Nelson, John M., Ph.D. Columbia University, New York City. *Professor of Organic Chemistry.* (2, 1923)
- Nelson, P. Mabel, M.S., Ph.D. Iowa State College, Ames. *Dean, Division of Home Economics.* (5, 1934)
- Nelson, Tell, M.A., M.D. 5434 Lakewood Ave., Chicago, Ill. (6, 1938)
- Nelson, Vietor E., M.S. Iowa State College, Ames. *Professor of Physiological Chemistry.* (2, 1924)
- Nelson, Warren O., M.S., Ph.D. Dept. of Anatomy, School of Medicine, Univ. of Iowa, Iowa City. *Professor of Anatomy.* (1, 1937)
- Neter, Erwin, M.D. Children's Hospital, 219 Bryant St., Buffalo, N. Y. *Attending Bacteriologist.* (6, 1937)
- Nettleship, Anderson, M.D. Fort Wayne Medical Laboratory, 347 W. Berry St., Fort Wayne, Ind. *Director.* (4, 1942)
- Neuberg, Carl, Ph.D., M.D. (h.c.), Med. Chem. D. (h.c.), Biol. D. (h.c.), Dr. Eng. (h.c.), LL.D. 905 Westend Ave., New York City. *Research Professor, New York University; Member or hon. member of the Academies of Science of Copenhagen, Göttingen, Leningrad, Lisbon, Lund, Prag, Romc and Upsala.* (2, 1944)
- Neumann, Charles, M.D.\* 2 Schuyler St., New Rochelle, N. Y. *First Assist. Resident Surgeon, New York Hospital; Assist. in Surgery, Cornell Univ. Med. Collegc.* (1, 1944)
- Neurath, Hans, Ph.D. School of Medicine, Duke University, Durham, N. C. *Associate Professor of Biochemistry.* (2, 1940; 6, 1944)
- Neuwelt, Frank, M.D. 504 Broadway, Gary, Ind. *Research Associate, Department of Gastro-intestinal Research, Michael Reese Hospital.* (1, 1940)
- Neuwirth, Isaac, Ph.D. 209 E. 23rd St., New York City. *Associate Professor of Pharmacology and Therapeutics, New York University College of Dentistry.* (2, 1924; 3, 1931)
- Nice, Leonard B., Ph.D. Chicago Medical School, 710 S. Wolcott Ave., Chicago, Ill. *Professor of Physiology and Pharmacology.* (1, 1921)
- Nicholas, John S., M.S., Ph.D. Osborn Zoological Laboratory, Yale University, New Haven, Conn. *Bronson Professor of Comparative Anatomy.* (1, 1927)
- Nicholson, Hayden C., M.S., M.D. 14 N. Roosevelt St., Falls Church, Va. *Major, A. U. S.* (1, 1932)
- Nickerson, John L., Ph.D.\* Columbia University, 630 W. 168th St., New York 32, N. Y. *Assistant Professor of Physiology.* (1, 1945)
- Nielet, Ben H., Ph.D. Bureau of Dairy Industry, U. S. Department of Agriculture, Beltsville, Md. *Senior Chemist.* (2, 1932)
- Nicoll, Paul A., Ph.D.\* Indiana University, Bloomington. *Assistant Professor of Physiology.* (1, 1945)
- Niemann, Carl G., Ph.D. California Institute of Technology, Pasadena 4, Calif. *Associate Professor, Organic Chemistry.* (2, 1940)
- Nigg, Clara, M.A., Ph.D. e/o E. R. Squibb & Sons, New Brunswick, N. J. (6, 1929)
- Nims, Leslie F., M.A., Ph.D. Yale University School of Medicine, 333 Cedar St., New Haven, Conn. *Assistant Professor of Physiology.* (1, 1940)
- Noble, Robert Laing, M.D., Ph.D. Research Institute of Endocrinology, McGill University, Montreal, Canada. *Research Assistant.* (1, 1941)
- Nord, F. F., Ph.D. Fordham University, Dept. of Organic Chemistry, New York City. *Professor of Chemistry.* (2, 1940)
- Norris, Earl R., Ph.D. University of Washington, Seattle. *Professor of Chemistry.* (2, 1938)
- Norris, L. C., Ph.D. Rice Hall, Cornell University, Ithaca, N. Y. *Professor of Nutrition; Secretary, School of Nutrition.* (2, 1939; 5, 1934)
- Northrop, J. H., M.A., Ph.D., Sc.D., LL.D. Rockefeller Institute for Medical Research, Princeton, N. J. *Member.* (2, 1938)
- Northup, David W., M.A., Ph.D. West Virginia University Medical School, Morgantown. *Associate Professor of Physiology.* (1, 1936)
- Novy, F. G., M.D., Sc.D., LL.D. 721 Forest Ave., Ann Arbor, Mich. *Dean Emeritus of the*

- Medical School and Professor Emeritus of Bacteriology, University of Michigan; Member, National Academy of Sciences.* (2, 1906)
- Nye, Robert N., M.D. Boston City Hospital, Boston, Mass. *Editor, New England Journal of Medicine.* (6, 1923)
- Oberst, Fred W., M.S., Ph.D. The Wm. S. Merrell Co., Lockland Station, Cincinnati, O. *Chief, Division of Biochemistry.* (2, 1936)
- Ochoa, Severo, M.D. Department of Chemistry, New York University College of Medicine, New York City 16. *Research Associate in Medicine.* (2, 1942)
- Ogden, Eric, M.R.C.S. (England), L.R.C.P. (London). University of Texas School of Medicine, Galveston. *Professor of Physiology and Clinical Physiologist, John Sealy Hospital.* (1, 1941)
- O'Hare, James P., M.D. 520 Commonwealth Ave., Boston, Mass. *Physician, Peter Bent Brigham Hospital; Assistant Professor of Medicine, Harvard Medical School.* (4, 1927)
- Ohlson, Margaret A., M.S., Ph.D. Dept. of Foods and Nutrition, Michigan State College, East Lansing. *Professor and Head, Department of Foods and Nutrition.* (5, 1945)
- Okey, Ruth, Ph.D. 1583 Life Sciences Bldg., University of California, Berkeley. *Professor of Home Economics and Biochemist, State Experiment Station.* (2, 1922; 5, 1932)
- Olcott, Harold S., M.S., Ph.D. Western Regional Research Laboratory, U. S. Department of Agriculture, Albany 6, Calif. *Senior Chemist.* (2, 1935)
- Olitsky, Peter K., M.D. Rockefeller Institute for Medical Research, 66th St. and York Ave., New York City. *Member.* (4, 1923; 6, 1917)
- Oliver, Jean Redman, M.D. Hoagland Laboratory, 335 Henry St., Brooklyn, N. Y. *Professor of Pathology, Long Island College of Medicine.* (1, 1924; 4, 1924)
- Oliver, Wade W., M.D. Hoagland Laboratory, 335 Henry St., Brooklyn, N. Y. *Professor of Bacteriology, Long Island College of Medicine.* (4, 1925)
- Olmsted, J. M. D., M.A., Ph.D. University of California, Berkeley. *Professor of Physiology.* (1, 1920)
- Olson, Carl, Jr., D.V.M., Ph.D. Massachusetts State College, Amherst. *Research Professor of Veterinary Science.* (4, 1937)
- Oddyke, David F., Ph.D.\* Western Reserve Medical School, Cleveland 6, O. *Senior Instructor in Physiology.* (1, 1945)
- Opie, Eugene L., M.D., Sc.D., LL.D. Rockefeller Institute for Medical Research, 66th St. and York Ave., New York 21, N. Y. *Member, National Academy of Sciences.* (1, 1906; 4, 1913; 6, 1923)
- Oppenheimer, Enid Tribe, 124 E. 61st St., New York City. *Instructor in Physiology, Columbia University.* (1, 1932)
- Oppenheimer, Ernst, M.D. Ciba Pharmaceutical Products, Inc., Lafayette Park, Summit, N. J. *Vice-President in charge of Medical Research.* (3, 1944)
- Oppenheimer, Morton Joseph, Ed.M., M.D. 3400 N. Broad St., Philadelphia, Pa. *Associate Professor of Physiology, Temple University School of Medicine.* (1, 1942)
- Orent-Keiles, Elsa, D.Sc. Bureau of Human Nutrition and Home Economics, U. S. Department of Agriculture, Beltsville, Md. *In Charge of Nutrition Investigations; Assistant Chief, Foods and Nutrition Division.* (2, 1935; 5, 1935)
- Ort, John M., Ph.D. 356 Raymond St., Rockville Centre, Long Island, N. Y.; American Pharmaceutical Company, New York City. *Director of Laboratories.* (2, 1932)
- Orten, James M., M.S., Ph.D. Wayne University College of Medicine, Detroit, Mich. *Associate Professor of Physiological Chemistry.* (2, 1936; 5, 1937)
- Orth, O. Sidney, M.S., Ph.D., M.D. University of Wisconsin Medical School, Madison. *Associate Professor of Pharmacology.* (1, 1942; 3, 1944)
- Osborne, Stafford L., B.P.E., M.S., Ph.D. Northwestern University Medical School, 303 E. Chicago Ave., Chicago, Ill. *Associate Professor of Physical Therapy.* (1, 1941)
- Oser, Bernard L., M.S., Ph.D. Food Research Laboratories, Inc., 48-14 Thirty-third St., Long Island City 1, N. Y. *Director.* (5, 1945)
- Oster, Robert H., Ph.D. University of Maryland Medical School, Greene and Lombard Sts., Baltimore. *Assistant Professor of Physiology.* (1, 1938)
- Osterberg, Arnold E., M.S., Ph.D. Mayo Clinic, Rochester, Minn. *Head, Clinical Biochemistry; Professor, Mayo Foundation.* (2, 1933)
- Osterhout, Marian I. Rockefeller Institute for Medical Research, 66th St. and York Ave., New York City 21. *Associate, Division of General Physiology.* (1, 1927)
- Osterhout, W. J. V., Ph.D. Rockefeller Institute, 66th St. and York Ave., New York City. *Member Emeritus of the Institute; Member of the National Academy of Sciences.* (1, 1910)
- Owen, Seward E., M.S., Ph.D. 418 So. 20th Ave., Maywood, Ill. *Major, S. E. Sn. Corps.* (1, 1933)
- Pace, Donald M., Ph.D.\* Dept. of Physiology and Pharmacology, College of Pharmacy, University of Nebraska, Lincoln. *Associate Professor of Physiology.* (1, 1944)
- Pack, George T., M.D. 139 E. 36th St., New York City 16. *Fellow in Cancer Research, Memorial Hospital.* (1, 1924)
- Packchanian, Ardzoony, Ph.D. School of Medicine, University of Texas, Galveston. *Associate Pro-*

- essor of Bacteriology and Tropical Medicine.* (6, 1943)
- Page, Irvine H., M.D. Cleveland Clinic Foundation, Euclid Ave. and 93rd St., Cleveland 6, O. Director of Research Division. (1, 1937; 2, 1932)
- Painter, Elizabeth E., Ph.D. Loyola Univ. School of Medicine, 706 S. Wolcott, Chicago 12, Ill. Assistant Professor of Physiology. (1, 1941)
- P'An, S. Y., M.D. Peiping Union Medical College, Peiping, China. Assistant in Pharmacology. (3, 1941)
- Pangborn, Mary C., Ph.D. 20 Morris St., Albany, N. Y. Senior Biochemist, New York State Department of Health, Division of Laboratories and Research. (2, 1941)
- Pappenheimer, Alwin M., Jr., Ph.D. 19th Medical General Laboratory, APO 5467, c/o Postmaster, San Francisco, Calif. Major, S.A.C., A.U.S. (2, 1941; 6, 1938)
- Pappenheimer, Alwin M., M.D. 5 Acacia St., Cambridge, Mass. Professor Emeritus of Pathology, Columbia University. (4, 1922)
- Park, Edwards A., M.D. Johns Hopkins Hospital, Baltimore, Md. Professor of Pediatrics, Johns Hopkins University. (4, 1923)
- Parker, George Howard, Sc.D. 16 Berkeley St., Cambridge, Mass. Professor of Zoology Emeritus, Harvard University; Member of the National Academy of Sciences. (1, 1900)
- Parker, Robert F., M.D. Lakeside Hospital, 2065 Adelbert Rd., Cleveland, O. Associate Professor of Medicine. (4, 1942; 6, 1935)
- Parkins, William M., M.A., Ph.D. School of Medicine, University of Pennsylvania, Philadelphia. Research Associate, Harrison Department of Surgical Research. (1, 1939)
- Parpart, Arthur K., Ph.D. Guyot Hall, Princeton University, Princeton, N. J. Associate Professor of Physiology. (1, 1937)
- Parr, Leland W., Ph.D. The George Washington University School of Medicine, 1335 H St., N.W. Washington, D. C. Professor of Bacteriology. (4, 1940)
- Parsons, Helen T., M.S., Ph.D. University of Wisconsin, Madison. Professor of Home Economics; In Charge of Purcell Research in Nutrition. (2, 1929; 5, 1933)
- Parsons, Robert J., M.D. University of Michigan, Ann Arbor. Assistant Professor of Pathology. (4, 1939)
- Paschkis, Karl E., M.D. 1025 Walnut St., Philadelphia, Pa. Chief of Clinic, Endocrine Clinic, Associate in Physiology, Associate in Medicine, Jefferson Medical College and Hospital. (1, 1942)
- Patterson, Thos. L., A.M., M.S., Ph.D., Sc.D. (hon.) Wayne University College of Medicine,
- 1512 St. Antoine St., Detroit, Mich. Research Professor of Physiology. (1, 1920)
- Paul, John R., M.D., A.M. 330 Cedar St., New Haven, Conn. Professor of Preventive Medicine, Yale University Medical School. (4, 1927; 6, 1937)
- Pearce, John Musser, M.D. Long Island College of Medicine, Hoagland Laboratory, 335 Henry St., Brooklyn, N. Y. Associate Professor of Pathology. (4, 1942)
- Pearce, Louise, M.D. Rockefeller Institute for Medical Research, Princeton, N. J. Associate Member in Pathology and Bacteriology. (3, 1915; 4, 1925)
- Pearcy, J. Frank, Ph.D., M.D. 471 Park Ave., New York City. (1, 1928)
- Pearse, Herman E., M.D. School of Medicine and Dentistry, University of Rochester, Crittenton Blvd., Rochester, N. Y. Associate Professor of Surgery. (4, 1932)
- Pearson, Paul B., Ph.D. A & M College of Texas, College Station. Professor of Nutrition; Nutritionist, Agricultural Experiment Station. (2, 1944; 5, 1940)
- Pease, Marshall C., Jr., M.D. Branefield Rd., R.F.D. 4, Ridgefield, Conn. (6, 1920)
- Pemberton, Ralph, M.S., M.D. University of Pennsylvania, Philadelphia. Professor of Medicine, Graduate School of Medicine. (5, 1933)
- Penfield, Wilder G., M.D., D.Sc. McGill University, Montreal, Que., Canada. Professor of Neurology and Neurosurgery. (1, 1932)
- Pennington, Mary Engle, Ph.D. 233 Broadway, New York 7, N. Y. Consultant in Connection with the Handling, Transportation and Storage of Perishables. (2, 1908)
- Peoples, S. Anderson, M.D. Baylor University College of Medicine, Houston, Texas. Professor of Pharmacology. (3, 1937)
- Perlman, Ely, M.D. The Hospital of the Rockefeller Institute for Medical Research, 66th St. & York Ave., New York. Research Fellow. (6, 1944)
- Perlzweig, William A., A.M., Ph.D. Box 3711, Duke Hospital, Durham, N. C. Professor of Biochemistry, Duke University; Biochemist, Duke Hospital. (2, 1924; 5, 1944)
- Permar, Howard H., M.D. Pathologie Laboratories, Mercy Hospital, Pittsburgh, Pa. Director of Laboratories. (4, 1925)
- Peters, John P., M.D. 123 Marvel Road, New Haven 15, Conn. Sterling Professor of Medicine, Yale University. (2, 1922)
- Petersen, William F., M.D. 1322 Astor St., Chicago, Ill. Professor of Pathology, University of Illinois. (3, 1923; 4, 1923)
- Peterson, William H., A.M., Ph.D. Biochemistry Building, University of Wisconsin, Madison. Professor of Biochemistry. (2, 1919; 5, 1936)

- Petroff, S. A., Ph.D., Sc.D. Sea View Hospital, West New Brighton, Staten Island, N. Y. *Director of Bacteriology and Immunology*. (6, 1926)
- Pett, L. B., M.D., Ph.D. Department of National Health and Welfare, Ottawa, Canada. *Director of Nutrition*. (2, 1937; 5, 1945)
- Peugnet, Hubert B., M.D. AAF School of Aviation Medicine, Randolph Field, Texas. (1, 1938)
- Pfeiffer, Carl C., Ph.D., M.D. Department of Pharmacology, University of Illinois, 1853 West Polk St., Chicago 12. *Professor of Pharmacology*. (3, 1938)
- Pfissner, Joseph J., Ph.D. Research Laboratories, Parke, Davis & Co., Detroit 32, Mich. *Research Chemist*. (1, 1931; 2, 1931)
- Phatak, Nilkanth M., M.S., Ph.D. North Pacific College of Oregon, School of Dentistry, Portland. *Associate Professor of Physiology, Pharmacology, and Research; and Instructor, Dept. of Pharmacology, University of Oregon Medical School, Portland. Captain, Sn. C.* (3, 1941)
- Phillips, Paul H., Ph.D. University of Wisconsin, Madison. *Professor of Biochemistry*. (2, 1940; 5, 1938)
- Phillips, Robert Allan, M.D. Rockefeller Institute for Medical Research, New York City. *Fellow*. (1, 1938)
- Pick, Ernst Peter, M.D. 19 E. 98th St., New York City. *Associate Pharmacologist to the Mt. Sinai Hospital; Clinical Professor of Pharmacology in Columbia University*. (3, 1940)
- Pierce, Harold B., M.S., Ph.D. College of Medicine, University of Vermont, Burlington. *Professor and Head of Physiological Chemistry*. (2, 1929; 5, 1933)
- Pierce, Harold Fisher, Ph.D., M.D. Veterans Administration Hospital, Newington, Conn. *Major, M.C.* (1, 1928)
- Pierce, Ira H., M.S., Ph.D. Univ. of Iowa, Iowa City. *Associate Professor of Pharmacology*. (3, 1933)
- Pike, Frank H., Ph.D. 437 W. 59th St., New York City 19. *Associate Professor of Physiology, Columbia University*. (1, 1907)
- Pilcher, J. Douglas, M.D. City Hospital, Scranton Road, Cleveland, O. *Associate Professor of Pediatrics, Western Reserve Medical School*. (1, 1912; 3, 1911)
- Pillemer, Louis, Ph.D. Inst. of Pathology, Western Reserve Univ., Cleveland, O. (6, 1942)
- Pincus, Gregory, M.S., Sc.D. Clark University, Worcester, Mass. *Visiting Professor of Experimental Zoology*. (1, 1935)
- Pinkerton, Henry, M.D. St. Louis University School of Medicine, St. Louis, Mo. *Professor of Pathology*. (4, 1931)
- Pinkston, James O., Ph.D. 6627 Heartwood Dr., Oakland, Calif. *Professor of Pharmacology, School of Medicine, American University of Beirut*. (1, 1936; 3, 1939)
- Pinson, Ernest A., Ph.D.\* Biophysics Branch, Aeromedical Laboratory, Wright Field, Dayton, O. *Major, Air Corps*. (1, 1943)
- Pittman, Martha S., A.M., Ph.D. Kansas State College, Manhattan. *Head of Department of Food Economics and Nutrition*. (5, 1933)
- Pitts, Robert F., Ph.D., M.D. Cornell Medical Center, 1300 York Ave., New York City. *Associate Professor of Physiology*. (1, 1934)
- Plass, Everett D., M.D. University Hospital, Iowa City, Iowa. *Professor and Head of Department of Obstetrics and Gynecology, State University of Iowa*. (2, 1922)
- Plotz, Harry, M.D. Army Medical Center, Army Medical School, Washington, D. C. *Colonel, Chief of the Division of Virus and Rickettsial Diseases; Chief of Service, Pasteur Institute, Paris, France*. (6, 1917)
- Pohlman, Augustus G., M.D. 4056 Farmouth Dr., Los Angeles, Calif. *Associate Clinical Professor, Department of Otolaryngology, University of Southern California School of Medicine*. (1, 1934)
- Pollack, Herbert, Ph.D., M.D. 598 Madison Ave., New York City 22. *Associate in Medicine and Physician in Charge of Metabolism Clinics, Mt. Sinai Hospital*. (1, 1933; 5, 1935)
- Pomerat, Charles Marc, Ph.D.\* University of Texas Medical School, Galveston. *Professor of Anatomy*. (1, 1944)
- Pond, Samuel E., A.M., Ph.D. 400 S. Main St., East Hartford, Conn. *Consulting Engineer, P. and W. A. Division, United Aircraft Corp.* (1, 1924)
- Ponder, Eric, M.D., Sc.D. The Nassau Hospital, Mineola, Long Island, N. Y. (1, 1931)
- Popper, Hans, Ph.D., M.D. University of Illinois College of Medicine, 1825 W. Harrison St., Chicago. *Director of Laboratories and of the Hektoen Institute for Medical Research of Cook County Hospital*. (4, 1942)
- Porter, Eugene L., A.M., Ph.D. University of Texas, Medical Branch, Galveston. *Professor of Physiology*. (1, 1913)
- Porter, Thelma, University of Chicago, Chicago, Ill. *Prof. and Head of Department of Home Economics*. (5, 1944)
- Porter, William Townsend, M.D., Sc.D., LL.D. Dover, Mass. *Professor Emeritus of Comparative Physiology, Harvard University*. (1, 1891)
- Potter, Truman S., M.D. Dartmouth Medical School, Hanover, N. H. (6, 1939)
- Potter, Van Rensselaer, M.S., Ph.D. McArdle Memorial Laboratory, University of W

- Richter, Curt P., Ph.D. Phipps Psychiatric Clinic, The Johns Hopkins Hospital, Baltimore, Md. Associate Professor of Psycho-biology, Johns Hopkins University. (1, 1924)
- Richter, Maurice N., M.D. 303 E. 20th St., New York City. Professor of Pathology, Columbia University, New York Post-Graduate Medical School; Director, Department of Pathology, New York Post-Graduate Medical School and Hospital. (4, 1931)
- Ricketts, Henry T., M.D. Dept. of Medicine, University of Chicago, Chicago, Ill. Associate Professor of Medicine. (1, 1940)
- Riddle, Oscar, Ph.D. Cold Spring Harbor, L. I., N. Y. Visiting Professor from the U. S. (in South America); Member of the National Academy of Sciences. (1, 1919)
- Riegel, Byron, A.M., Ph.D. Department of Chemistry, Northwestern University, Evanston, Ill. Associate Professor. (2, 1942)
- Riegel, Cecilia, M.S., Ph.D. Room 563, University Hospital, Philadelphia, Pa. Research Associate, Department of Research Surgery, University of Pennsylvania School of Medicine. (2, 1938)
- Ries, Ferd A., M.D. 825 E. 41st St., Baltimore, Md. Instructor in Neurology, Johns Hopkins University. (1, 1933)
- Rigdon, R. H., M.D. Univ. of Arkansas School of Medicine, Little Rock. Professor of Pathology. (4, 1941)
- Riggs, Lloyd K., Ph.D. % Kraft Cheese Co., 500 Peshtigo Court, Chicago, Ill. Director of Research. (2, 1929)
- Rinehart, James F., M.D. University of California Medical School, Parnassus and Third Aves., San Francisco. Professor of Pathology. (4, 1933)
- Ring, Gordon C., M.A., Ph.D. Physiology Dept., Ohio State Univ., Columbus. (1, 1933)
- Rioch, David McKenzie, M.D. Chestnut Lodge Sanitarium, 500 W. Montgomery Ave., Rockville, Md. Director of Research. (1, 1931)
- Rittenberg, David, Ph.D. 630 W. 168th St., New York City. Assistant Professor, College of Physicians and Surgeons, Columbia University. (2, 1939)
- Ritzman, E. G., A.M., Science (hon.). University of New Hampshire, Durham. Research Professor. (5, 1933)
- Rivers, T. M., M.D., Sc.D. The Hospital of the Rockefeller Institute for Medical Research, 66th St. and York Ave., New York City. Director of the Hospital; Member of the National Academy of Sciences. (4, 1925; 6, 1921)
- Robb, Jane Sands, Sc.D., M.D. College of Medicine, Syracuse University, 761 Irving Ave., Syracuse, N. Y. Associate Professor of Pharmacology. (1, 1924)
- Robbins, Benjamin Howard, M.S., M.D. Vanderbilt Univ. School of Medicine, Nashville, Tenn. Associate Professor of Pharmacology. (3, 1936)
- Roberts, Edward F., M.D., Ph.D. Fourth Service Command, Medical Laboratory, Fort McPherson, Ga. (6, 1932)
- Roberts, Lydia J., Ph.D. University of Chicago, Chicago, Ill. Professor and Chairman of Department of Home Economics. (5, 1933)
- Robertson, Elizabeth Chant, M.D., M.A., Ph.D. University of Toronto, Toronto, Canada. Research Fellow in Pediatrics. (5, 1939)
- Robertson, Oswald H., M.D. University of Chicago, Chicago, Ill. Professor of Medicine. (4, 1932)
- Robinson, Charles Summers, Ph.D. Medical School, Vanderbilt University, Nashville, Tenn. Professor of Biochemistry. (2, 1925)
- Robinson, Elliott S., M.D., Ph.D. 3034 E Buchanan St., Arlington, Va. Lt. Col., M.C. (1935)
- Robinson, G. Canby, M.D., Sc.D., LL.D. Johns Hopkins Hospital, Baltimore, Md. Lecturer in Medicine, Johns Hopkins University. (1, 1912; 3, 1921)
- Robinson, George Henry, Ph.D. 320 E. North Ave., N. S., Pittsburgh, Pa. Bacteriologist, Wm. H. Singer Research Laboratory and Allegheny General Hospital; Lecturer in Bacteriology, University of Pittsburgh School of Medicine. (4, 1930)
- Robinson, Howard W., M.S., Ph.D. Broad and Ontario Sts., Philadelphia, Pa. Professor of Physiological Chemistry, Temple University School of Medicine. (2, 1929)
- Robinson, Sid, Ph.D. Indiana University Medical School, Bloomington. Associate Professor of Physiology. (1, 1941)
- Robscheit-Robbins, F. S., Ph.D. University of Rochester School of Medicine and Dentistry, Rochester, N. Y. Associate in Pathology. (1, 1925; 4, 1930)
- Rodbard, Simon, Ph.D. Cardiovascular Dept., Michael Reese Hospital, 29th and Ellis Aves., Chicago, Ill. (1, 1942)
- Roe, Joseph Hyram, M.A., Ph.D. George Washington University School of Medicine, Washington, D. C. Professor of Biochemistry. (2, 1927; 5, 1933)
- Roeder, Kenneth D., M.A. Tufts College, Medford, Mass. Associate Professor of Biology. (1, 1942)
- Roepke, Martin Henry, Ph.D. University Farm, St. Paul, Minn. Professor, Veterinary Medicine. (3, 1937)
- Rogers, Charles G., A.M., Ph.D., Sc.D. Oberlin College, Oberlin, O. Professor of Comparative Physiology. (1, 1911)

- Rogers, Fred T., A.M., Ph.D., M.D. Dallas Medical and Surgical Clinic, 4105 Live Oak St., Dallas 1, Texas. (1, 1917)
- Rogoff, Julius M., Ph.G., M.D., Sc.D. School of Medicine, University of Pittsburgh, Pittsburgh, Pa. Professor of Endocrinology. (1, 1916; 3, 1916)
- Ronzoni, Ethel, M.A., Ph.D. Washington University Medical School, St. Louis 4, Mo. Assistant Professor of Biological Chemistry. (2, 1923)
- Root, Howard F., M.D. 44 Dwight St., Brookline, Mass. Instructor in Medicine, Harvard Medical School. (5, 1933)
- Root, Walter S., Ph.D. College of Physicians and Surgeons, Columbia University, 630 W. 168th St., New York City. Associate Professor of Physiology. (1, 1932)
- Rosahn, Paul D., M.D. 92 Grand St., New Britain, Conn. Pathologist, New Britain General Hospital; Assistant Clinical Professor of Pathology, Yale University School of Medicine, New Haven. (4, 1934)
- Rose, Anton Richard, M.S., Ph.D. Box 176, Edgewater, N. J. Biochemist, Prudential Insurance Company of America. (2, 1916; 5, 1933)
- Rose, William C., Ph.D. University of Illinois, Urbana. Professor of Biochemistry and Acting Head of the Chemistry Department; Member, National Academy of Sciences. (2, 1912; 5, 1933)
- Rosenblueth, Arturo, M.D. Instituto Nacional de Cardiología, Calzada de la Piedad 300, Mexico D.F., Mexico. (1, 1932)
- Rosenfeld, Morris, M.D. Johns Hopkins School of Medicine, Baltimore, Md. Associate in Pharmacology and Experimental Therapeutics. Captain, M.C. (3, 1934)
- Rosenow, Edward C., M.D., hon. LL.D. and D.Sc. Mayo Clinic, Rochester, Minn. (4, 1913; 6, 1915)
- Rosenthal, Sanford M., M.D. National Institute of Health, Washington, D. C. Senior Pharmacologist, U. S. Public Health Service. (3, 1925)
- Rosenthal, S. R., M.D., Ph.D. University of Illinois College of Medicine, Chicago. Assistant Professor of Bacteriology and Public Health in Dept. of Pathology and Bacteriology; Director, Tice Laboratory for B. C. G. Vaccination against Tuberculosis, Municipal Tuberculosis Sanatorium. (4, 1941)
- Ross, Joseph F., M.D. The Robert Dawson Evans Memorial, 65 E. Newton St., Boston, Mass. Member of the Department; Physician, Massachusetts Memorial Hospital; Assistant Professor of Medicine, Boston University School of Medicine; Welch Fellow of Internal Medicine of the Division of Medical Sciences of the National Research Council. (4, 1941)
- Ross, William F., Ph.D. Shell Oil Company, P. O. Box 711, Martinez, Calif. Chief Research Chemist. (2, 1940)
- Roth, George B., M.D. George Washington Univ. 3814 Tea St., N.W., Washington 7, D. C. Emeritus Professor of Pharmacology. (1, 1914; 3, 1911)
- Roth, Grace M., M.S., Ph.D. Mayo Clinic, Rochester, Minn. Associate in Clinical Physiology. (1, 1939)
- Roth, Paul, M.D. Battle Creek Sanitarium, Battle Creek, Mich. Director of Physical Therapy. (1, 1929; 5, 1933)
- Rothmund, Paul W. K., Dipl.-Ing., Dr.-Ing. (Munich). Antioch College, Yellow Springs, O. Associate Professor of Biochemistry, and Research Chemist, The C. F. Kettering Foundation, Antioch College; Associate Professor (Non-resident), Department of Chemistry, Ohio State University. (2, 1940)
- Rous, Peyton, M.D., Sc.D. Rockefeller Institute for Medical Research, York Ave. at 66th St., New York City. Member; Member of the National Academy of Sciences. (4, 1913)
- Routh, Joseph I., M.S., Ph.D. Chemistry Department, State University of Iowa, Iowa City. Assistant Professor of Biochemistry. (2, 1942)
- Rovestine, Emery Andrew, M.D. 477 First Ave., New York, N. Y. Professor of Anesthesia, New York University; Director, Division of Anesthesia, Bellevue Hospital. (3, 1944)
- Rountree, Jennie I., M.S., Ph.D. University of Washington, Seattle. Professor of Home Economics. (5, 1933)
- Rountree, L. G., M.D., Sc.D., F.A.C.P. Temp. address: 4701 Connecticut Ave., N.W., Washington, D. C. Director, Philadelphia Institute for Medical Research; Colonel, Medical Reserve; Research Clinician, Philadelphia General Hospital; Chief, Medical Division, Selective Service, National Headquarters, Washington, D. C. (1, 1911; 2, 1910; 3, 1908; 4, prior to 1920)
- Rubenstein, Boris B., M.A., M.D., Ph.D. Edgewood Arsenal, Edgewood, Md. Captain, Medical Research Lab. (1, 1934)
- Rubin, Morton A., Ph.D. 3732 Gunston Rd., Alexandria, Va. Captain, Signal Corps, Office of the Chief Signal Officer, Military Personnel Division, Washington, D. C. (1, 1940)
- Ruch, Theodore C., M.A., Ph.D. Yale University School of Medicine, New Haven, Conn. Assistant Professor of Physiology. (1, 1933)
- Rusch, Harold Paul, M.D. University of Wisconsin Medical School, McArdle Memorial Laboratory, Madison 6. Professor of Oncology. (4, 1940)
- Russell, Walter C., Ph.D. New Jersey Agricultural Experiment Station and Rutgers University, New Brunswick. Biochemist in

- and Professor of Agricultural Biochemistry.* (2, 1932; 5, 1933)
- Ryan, Andrew Howard, M.D. Chicago Medical School, 710 S. Wolcott Ave., Chicago, Ill. *Associate Professor of Physiology and Pharmacology.* (1, 1912)
- Sabin, Florence R., M.D., Sc.D. 1333 E. 10th Ave., Denver 3, Colo. *Member Emeritus, Rockefeller Inst.; Member of National Academy of Sciences.* (1, 1923)
- Sachs, Ernest, M.D. 97 Arundel Pl., St. Louis, Mo. *Professor of Clinical Neurological Surgery, Washington University Medical School.* (1, 1910)
- Sacks, Jacob, Ph.D., M.D. Endo Products, Inc., 84-40, 101st St., Richmond Hill, N. Y. *Pharmacologist.* (3, 1933)
- Sah, Peter P. T., M.S., Ph.D. Department of Chemistry, Fu Jen University, Peiping, China; *Professor of Chemistry; Lecturer in Pharmacology, Peiping Union Medical College.* (3, 1941)
- Sahyun, Melville, A.M., Ph.D. Frederick Stearns & Co., 6533 E. Jefferson St., Detroit, Mich. *Vice President and Director of Research.* (2, 1932)
- Salmon, W. D., A.M. Alabama Polytechnic Institute, Auburn. *Animal Nutritionist.* (2, 1929; 5, 1933)
- Salter, William T., M.D. Yale School of Medicine, 333 Cedar St., New Haven, Conn. *Professor of Pharmacology.* (1, 1933; 3, 1942; 5, 1934)
- Sammis, Florence E., M.D. 136 E. 58th St., New York City. (6, 1943)
- Sampson, John J., M.D. Baxter General Hospital, Spokane, Wash. *Major M.C.* (1, 1932)
- Sampson, Myra, A.M., Ph.D. Smith College, Northampton, Mass. *Professor and Chairman of Department of Zoology.* (5, 1935)
- Samuels, Leo T., Ph.D. University of Utah Medical School, Salt Lake City. *Professor and Head of Dept. of Biochemistry.* (2, 1941; 3, 1937)
- Sandels, Margaret R., A.M., Ph.D. Florida State College for Women, Tallahassee. *Dean of School of Home Economics; Professor of Nutrition.* (5, 1933)
- Sandford, Irene, Ph.D. Billings Hospital, University of Chicago, Chicago, Ill. *Assistant Professor of Medicine.* (2, 1925; 5, 1933)
- Sandow, Alexander, Ph.D.\* Washington Square College, New York University, New York 3, N. Y. *Assistant Professor of Biology.* (1, 1945)
- Sandweiss, David J., M.D.\* 9739 Dexter Ave., Detroit, Mich. *Instructor in Clinical Medicine, Wayne University College of Medicine; Physi-*
- cian, Harper Hospital (OPD); Attending Physician Gastroenterology and Gastroscopy, North End Community Fund Clinic. (1, 1944)
- Sanford, Arthur H., A.M., M.D. Clinical Laboratories, Mayo Clinic, Rochester, Minn. *Head, Division of Clinical Laboratories.* (6, 1920)
- Santos, Francisco O., M.S., Ph.D. University of the Philippines, Los Banos, Laguna. *Professor and Head of Department of Agricultural Chemistry, College of Agriculture.* (5, 1936)
- Saphir, Otto, M.D. Michael Reese Hospital, 29th St. and Ellis Ave., Chicago 16, Ill. *Pathologist, Michael Reese Hospital; Professor of Pathology, University of Illinois Medical School.* (4, 1927)
- Sappington, Samuel W., M.D., D.Sc. P. O. Box 81, Bryn Mawr, Pa. *Professor of Pathology, Hahnemann Hospital.* (6, 1913)
- Saslow, George, Ph.D., M.D. Department of Neuropsychiatry, Washington University Medical School, 640 South Kingshighway, St. Louis, Mo. *Assistant Professor of Psychiatry.* (1, 1936)
- Satterfield, G. Howard, A.M. State College of Agriculture and Engineering, University of North Carolina, Raleigh. *Professor of Biochemistry.* (2, 1944; 5, 1941)
- Saul, Leon Joseph, M.A., M.D. Three Walls Farm, Ridley Creek Rd., Media, Pa. (1, 1933)
- Saunders, Felix, Ph.D. 231 Playa del Sur, La Jolla, Calif. (2, 1938)
- Sawyer, Margaret E. MacKay, M.A., Ph.D. 142 Lower Albert St., Kingston, Ontario, Canada. (1, 1935)
- Sawyer, Wilbur A., M.D. 3927 Idaho Ave., N.W., Washington, D. C. *Director of Health, United Nations Relief and Rehabilitation Administration.* (4, 1930; 6, 1935)
- Saxton, John A., Jr., M.D. Snodgrass Laboratory of Pathology and Bacteriology, 1426 Carroll St., St. Louis, Mo. *Assistant Professor of Pathology, Washington University School of Medicine; Medical Director, Pathology, Hospital Division, City of St. Louis.* (4, 1944)
- Scammon, Richard E., M.A., Ph.D. 172 S. E. Bedford St., Minneapolis, Minn. *Distinguished Service Professor in the Graduate School, University of Minnesota.* (1, 1923)
- Schales, Otto, D.Sc. Oehsner Clinic, Prytania and Aline Sts., New Orleans, La. *Director of Chemical Research, Oehsner Foundation; Director of the Biochemical Laboratory, Oehsner Clinic.* (2, 1944)
- Scharles, Frederick H., M.D. 1405 Bryant Bldg., Kansas City, Mo. (5, 1935)
- Schattenberg, Herbert John, M.S., M.D. Bureau of Laboratories, Medical and Surgical Memorial Hospital, 205 Camden St., San Antonio, Texas. *Director.* (4, 1940)

- Schenken, John R., M.D. Louisiana State University School of Medicine, New Orleans. *Professor of Pathology and Bacteriology.* (4, 1942)
- Scherp, Henry W., M.S., Ph.D. University of Rochester Medical School, 260 Crittenden Blvd., Rochester, N. Y. *Assistant Professor of Immunochemistry.* (6, 1940)
- Schick, Bela, M.D. 17-E. 84th St., New York City. *Pediatrician, Mt. Sinai Hospital.* (6, 1924)
- Schiffrin, Milton J.,\* M.S., Ph.D. *Captain, Altitude Training Section, WWAAAB, Walla Walla, Wash.* (1, 1943)
- Schlenk, Fritz, Ph.D. University of Texas; M. D. Anderson Hospital of Cancer Research, Houston. *Biochemist.* (2, 1942)
- Schlesinger, M. J., Ph.D., M.D. Beth Israel Hospital, 330 Brookline Ave., Boston, Mass. *Associate in Pathology, Harvard Medical School; Director of Pathology, Beth Israel Hospital.* (4, 1942; 6, 1921)
- Schlomovitz, Benjamin H., M.D. 1210 Majestic Bldg., 231 W. Wisconsin Ave., Milwaukee, Wis. *Director, Clinical and Research Laboratory, Veterans Administration Hospital, Wood, Wisconsin.* (1, 1919)
- Schlumberger, Hans G., M.D. University of Pennsylvania Medical School, Philadelphia, Pa. *Instructor in Pathology.* (4, 1945)
- Schmeisser, Harry C., M.D. University of Tennessee, Memphis. *Professor of Pathology.* (4, 1937)
- Schmidt, Carl F., M.D. Medical School, University of Pennsylvania, Philadelphia. *Professor of Pharmacology.* (1, 1929; 3, 1924)
- Schmidt, Carl L. A., M.S., Ph.D. 1557 Life Sciences Bldg., University of California, Berkeley. *Professor of Biochemistry; Chairman of the Division of Biochemistry.* (2, 1919)
- Schmidt, C. Robert, Ph.D., M.D. Hertzler Clinic, Halstead, Kan. *Resident Surgeon, Major (MC) A.U.S.* (1, 1940)
- Schmidt, Gerhard, M.D. Boston Dispensary, 25 Bennett St., Boston, Mass. *Senior Research Fellow, Tufts College Medical School.* (2, 1939)
- Schmidt, Leon H., M.S., Ph.D. Christ Hospital, Institute for Medical Research, Cincinnati, O. *Director of Research; Assistant Professor of Biological Chemistry, College of Medicine, University of Cincinnati.* (2, 1936)
- Schmitt, Francis Otto, Ph.D. Dept. of Biology and Public Health, Massachusetts Institute of Technology, Cambridge. *Professor of Biology.* (1, 1930)
- Schnedorf, Jerome G., M.D., Ph.D. 801 Simpson St., Evanston, Ill. *Captain, M.C.* (1, 1941)
- Schneider, Edward C., Ph.D., Sc.D., M.P.E. 25 Gardan Place, Middletown, Conn. *University Professor Emeritus, Wesleyan University.* (1, 1912; 2, 1912)
- Schoenbach, Emanuel B., M.D. Meningocele Commission, Johns Hopkins School of Hygiene, 615 N. Wolfe St., Baltimore, Md. (6, 1941)
- Schoepfle, Gordon M., A.M., Ph.D.\* Washington University, School of Medicine, St. Louis, Mo. *Instructor in Physiology.* (1, 1943)
- Schradeck, Constant E., M.D. 65 Hazard Ave., Providence, R. I. *Director, Pathological Department, Homeopathic Hospital of Rhode Island.* (6, 1921)
- Schreiner, Oswald, M.S., Ph.D. Bureau of Plant Industry, U. S. Department of Agriculture, Washington 25, D. C. *Chief, Division of Soil Fertility Investigations.* (2, 1908)
- Schroeder, E. F., M.S., Ph.D. G. D. Seafie & Co., P. O. Box 5110, Chicago 80, Ill. *Research Biochemist.* (2, 1938)
- Schuck, Cecelia, Ph.D. Purdue University, Lafayette, Ind. *Professor of Nutrition, Department of Home Economics.* (5, 1941)
- Schnitz, Edwin William, M.D. 743 Cooksey Lane, Stanford University, Calif. *Professor of Bacteriology and Experimental Pathology.* (4, 1927; 6, 1928)
- Schultz, Mark P., A.M., M.D. National Institute of Health, Bethesda, Md. *Surgeon, U. S. Public Health Service.* (6, 1933)
- Schultz, W. H., Ph.D. 3102 18th St., N.W., Washington, D. C. *Professor of Pharmacology, Emeritus, University of Maryland.* (1, 1907; 3, 1909)
- Schultze, Max O., Ph.D. Department of Chemistry, University of Pittsburgh, Pittsburgh, Pa. *Research Fellow, Buch Foundation.* (2, 1938)
- Schwartz, Erich W., M.D. 1225 Talbert St., S. E., Washington, D. C. (3, 1920)
- Schweizer, Malvina, Ph.D.\* Washington Square College of Arts and Sciences, New York University, New York, N. Y. *Instructor in Biology.* (1, 1944)
- Scott, Charles Covert, Ph.D., M.D. The Lilly Research Laboratories, Eli Lilly and Company, Indianapolis 6, Ind. *Pharmacologist.* (3, 1945)
- Scott, David Alymer, M.A., Ph.D. Connaught Laboratories, University of Toronto, Toronto 5, Ontario, Canada. *Research Member.* (2, 1935)
- Scott, Ernest L., Ph.D. 64 South St., Bogota, N.J. *Associate Professor of Physiology, Emeritus, Columbia University.* (1, 1914; 2, 1915)
- Scott, Frederick Hughes, Ph.D., Sc.D. University of Minnesota, Minneapolis. *Professor of Physiology, Emeritus.* (1,

- Scott, John C., Ph.D. Hahnemann Medical College, Philadelphia, Pa. *Professor of Physiology and Head of the Department.* (1, 1936)
- Scott, R. W., A.M., M.D. City Hospital, Cleveland, O. *Professor of Clinical Medicine, Western Reserve University; Physician-in-chief, Cleveland City Hospital.* (1, 1917; 3, 1917)
- Scott, V. Brown, Ph.D., M.D. Inlow Clinic, Shelbyville, Ind. *Internist, Division of Medicine.* (1, 1941)
- Scott, W. J. Merle, M.D. University of Rochester Medical School, Rochester, N. Y. *Associate Professor of Surgery.* (4, 1925)
- Scott, W. W., M.D.\* University Clinics, University of Chicago, Chicago, Ill. *Instructor in Surgery.* (1, 1943)
- Scudi, John Vincent, Ph.D. Dept. of Pharmacology, Columbia Univ., 630 West 168th St., New York 32, N. Y. (2, 1942; 5, 1945)
- Seager, Lloyd D., M.S., M.D. Woman's Medical College of Pennsylvania, East Falls, Philadelphia. *Professor of Pharmacology and Toxicology.* (3, 1939)
- Sealock, Robert R., Ph.D. Iowa State College, Ames. *Associate Professor of Chemistry.* (2, 1940; 5, 1941)
- Seastone, C. V., Jr., M.D. University of Wisconsin Medical School, Madison. *Associate Professor of Medical Bacteriology.* (6, 1939)
- Sebrell, W. H., Jr., M.D. National Institute of Health, Bethesda, Md. *Chief, Division of Physiology.* (2, 1938; 5, 1937)
- Seeoff, David P., M.D. 1970 Daly Ave., Bronx, New York City. (4, 1927)
- Seegal, David, M.D. Welfare Island, New York City. *Director, Research and Clinical Service, First Division, Goldwater Memorial Hospital; Associate Professor of Medicine, Columbia University.* (6, 1930)
- Seegers, Walter H., Ph.D. Wayne University College of Medicine, Detroit 26, Mich. *Associate Professor.* (2, 1941)
- Seavers, Maurice Harrison, Ph.D., M.D. University of Michigan School of Medicine, Ann Arbor. *Professor of Pharmacology and Chairman of the Department.* (1, 1933; 3, 1930)
- Seibert, Florence B., Ph.D., Se.D., LL.D. Henry Phipps Institute, University of Pennsylvania, 7th and Lombard Sts., Philadelphia. *Associate Professor of Biochemistry.* (2, 1925)
- Seidell, Atherton, M.S., Ph.D. 2301 Connecticut Ave., Washington, D. C. *Special Expert, National Institute of Health.* (2, 1924)
- Seifter, Joseph, M.D. Wyeth Institute of Applied Biochemistry, Philadelphia, Pa. *Chief Pharmacologist.* (3, 1940)
- Selkurt, Ewald E., Ph.D.\* School of Medicine, Western Reserve University, Cleveland 6, O. *Senior Instructor in Physiology.* (1, 1945)
- Selle, Wilber Arthur, Ph.D. Medical School, University of Texas, Galveston. *Professor of Physiology.* (1, 1938)
- Selye, Hans, M.D., Ph.D., D.Sc., F.R.S.(e.) Inst. of Experimental Medicine and Surgery, Univ. of Montreal, Montreal, Canada. *Professor and Director.* (1, 1934)
- Sendroy, Julius, Jr., M.A., Ph.D. Mercy Hospital, 2537 Prairie Ave., Chicago, Ill. *Professor of Chemistry and Chairman of the Department of Experimental Medicine, Loyola University School of Medicine.* (2, 1928)
- Sevag, M. G., Ph.D. Department of Bacteriology, University of Pennsylvania School of Medicine, Philadelphia. *Assistant Professor of Biochemistry in Bacteriology.* (6, 1941)
- Sevringshaus, Elmer L., M.A., M.D. Wisconsin General Hospital, Madison. *Professor of Medicine, University of Wisconsin; Consultant in Clinical Chemistry, Wisconsin Psychiatric Institute; Chemist to Wisconsin General Hospital.* (2, 1923; 5, 1939)
- Shaffer, Morris F., D. Phil. Department of Pathology and Bacteriology, School of Medicine, Tulane University of Louisiana, New Orleans. *Associate Professor.* (4, 1939; 6, 1937)
- Shaffer, Philip A., Ph.D. Washington University Medical School, St. Louis 4, Mo. *Professor of Biological Chemistry and Dean of the School of Medicine; Member, National Academy of Sciences.* (1, 1906; 2, 1906; 5, 1935)
- Shannon, James A., M.D., Ph.D. Welfare Island, New York City. *Director of Research Service, Third (New York University) Medical Division, Goldwater Memorial Hospital, Department of Pharmacology, New York University College of Medicine; Professor of Pharmacology.* (1, 1933; 3, 1945)
- Shapiro, Herbert, A.M., Ph.D. Radiation Laboratory M.I.T., Cambridge, Mass. *Staff Member.* (1, 1937)
- Sharpless, George R., D.Sc. Henry Ford Hospital, Detroit, Mich. *Associate in Nutrition Research.* (5, 1942)
- Shaw, Myrtle, M.S., Ph.D. 11 S. Lake Ave., Albany, N. Y. *Senior Bacteriologist, Division of Laboratories and Research, New York State Department of Health.* (6, 1937)
- Shay, Harry, M.D.\* Samuel S. Fels Fund, Medical Tower, Philadelphia, Penna. *Director, Medical Research Laboratory.* (1, 1944)
- Shear, Murray, J., Ph.D. National Cancer Institute, Bethesda, Md. *Principal Biochemist.* (2, 1930)
- Sheard, Charles, A.M., Ph.D. Mayo Foundation, Rochester, Minn. *Chief of the Division of Physics and Biophysical Research and Professor of Physiological Optics and Biophysics, University of Minnesota.* (1, 1925)

- Sheehan, Donal, M.D., D.Sc. New York University College of Medicine, First Ave., New York City. *Professor of Anatomy and Director of Anatomical Laboratories.* (1, 1938)
- Shemin, David, A.M., Ph.D. Columbia University, College of Physicians and Surgeons, 630 W. 168th St., New York City. *Associate in Biochemistry.* (2, 1944)
- Sheppard, Fay, M.S. University of Oklahoma Medical School, Oklahoma City. *Instructor in Biochemistry.* (2, 1936)
- Sherman, Henry C., A.M., Ph.D., Sc.D. Columbia University, New York City. *Mitchell Professor of Chemistry and Executive Officer of the Department of Chemistry; Member, National Academy of Sciences.* (1, 1923; 2, 1906; 5, 1933)
- Sherwin, Carl Paxson, Sc.D., M.D., Dr.P.H., LL.D. 6 Carstensen Rd., Scarsdale, N. Y. *Director of Metabolic Service, St. Vincent's Hospital; Associate Physician, French Hospital.* (1, 1919; 2, 1917)
- Sherwood, Noble P., Ph.D., M.D. 1801 Indiana St., Lawrence, Kan. *Professor of Bacteriology, University of Kansas.* (6, 1928)
- Sherwood, Thomas Cecil, M.A., Ph.D. 2639 Napoleon Ave., New Orleans, La. *House Physician, Southern Baptist Hospital.* (1, 1938)
- Shideman, Frederick E., Ph.D. Dept. of Pharmacology, University of Michigan, Ann Arbor. *Instructor of Pharmacology.* (3, 1944)
- Shimkin, Michael Boris, M.D. U. S. Public Health Service, National Cancer Institute, Bethesda, Md. *Passed Assistant Surgeon.* (4, 1940)
- Shipley, Reginald A., M.D.\* Western Reserve University School of Medicine, Cleveland 6, O. *Assistant Professor of Medicine.* (1, 1945)
- Shipley, Robert E., M.D.\* Lilly Laboratory for Clinical Research, Indianapolis City Hospital, Indianapolis, Ind. (1, 1945)
- Shlaer, Simon, M.A., Ph.D. Columbia University, New York City. *Research Associate in Biophysics.* (1, 1938)
- Shock, Nathan W., Ph.D. Unit on Gerontology, U. S. Public Health Service, Baltimore City Hospitals, Baltimore, Md. *Senior Physiologist, U. S. Public Health Service, National Institute of Health, Bethesda, Md.* (1, 1942)
- Shoemaker, Harold A., M.S., Ph.D. University of Oklahoma School of Medicine, 801 E. 13th St., Oklahoma City. *Assistant Dean; Professor of Pharmacology.* (3, 1941)
- Shohl, Alfred T., M.D. 300 Longwood Ave., Boston, Mass. *Research Associate in Pediatrics, Harvard Medical School.* (2, 1922; 5, 1933)
- Shope, Richard E., M.D. Department of Animal and Plant Pathology, The Rockefeller Institute, Princeton, N. J. *Member.* (4, 193-)
- Shorr, Ephraim, M.D. The New York Hospital, 525 East 68th St., New York City. *Associate Professor of Medicine, Cornell University Medical College; Assistant Attending Physician, The New York Hospital.* (1, 1931; 3, 1942)
- Shwartzman, Gregory, M.D. 230 E. 50th St., New York City. *Head of Department of Bacteriology, Mount Sinai Hospital; Clinical Professor of Bacteriology, Columbia University.* (4, 1929; 6, 1930)
- Sichel, F. J. M., Sc.M., Ph.D. College of Medicine, University of Vermont, Burlington. *Associate Professor of Physiology.* (1, 1939)
- Sickles, Grace M., B.A. 2201 Twelfth St., Troy, N. Y. *Associate Bacteriologist, Division of Laboratories and Research, New York State Department of Health.* (6, 1932)
- Sickles, Gretchen R., A.B. Division of Laboratories and Research, New York State Department of Health, Albany, N. Y. *Assistant Bacteriologist.* (6, 1937)
- Siebert, Walter J., M.D. DePaul Hospital, St. Louis 13, Mo. *Director of Laboratories and Pathologist of DePaul and Lutheran Hospitals, St. Louis, and of St. Joseph Hospital, Alton, Ill., St. Elizabeth's Hospital, Belleville, Ill., St. Francis Hospital, Washington, Mo.* (4, 1932)
- Silberberg, Martin, M.D. Snodgrass Laboratory of Pathology, City Hospital, 1426 Carroll St., St. Louis 4, Mo. *Instructor in Pathology, Washington University, School of Medicine.* (4, 1944)
- Silberberg, Ruth, M.D. Jewish Hospital, St. Louis, Mo. *Acting Pathologist, Instructor in Pathology, Washington University Medical School.* (4, 1944)
- Silvette, Herbert, M.S., Ph.D. University of Virginia Medical School, University. *Acting Head of Pharmacology.* (1, 1933; 3, 1940)
- Simon, Frank A., M.D. 812 Heyburn Bldg., Louisville, Ky. (6, 1934)
- Simonds, James P., Ph.D., M.D. Northwestern University Medical School, 303 E. Chicago Ave., Chicago, Ill. *Professor of Pathology.* (4, prior to 1920)
- Simonson, Ernst, M.D. c/o Laboratory of Physiological Hygiene, Stadium South Tower, University of Minnesota, Minneapolis 14. *Associate Professor of Physiological Hygiene and of Physiology.* (1, 1941)
- Sinclair, Robert Gordon, Ph.D., F.R.S.C. Queen's University, Kingston, Ont., Canada. *Professor of Biochemistry.* (2, 1931)
- Sizer, Irwin W., Ph.D.\* Massachusetts Institute of Technology, Cambridge. *Associate Professor of Physiology.* (1, 1944)
- Slaughter, Donald, M.D. Southwestern College, 2211 Oak Lawn, Dallas, Tex. *Students, Professor of Pharmacology.*

- man of the Department of Physiology and Pharmacology.* (3, 1938)
- Slonaker, James R., Ph.D. 334 Kingsley Ave., Palo Alto, Calif. Professor of Physiology, Leland Stanford Junior University. (1, 1917)
- Smadel, Joseph Edwin, M.D. 3-30 Parsons Blvd., Malba, Long Island, N. Y. Associate Member; Asst. Physician, Rockefeller Hospital. (4, 1940; 6, 1937)
- Small, James C., M.D. 133 S. 36th St., Philadelphia, Pa. Instructor in Medicine, Graduate School of Medicine, University of Pennsylvania. (4, 1927)
- Smetana, Hans, M.D. College of Physicians and Surgeons, 630 W. 168th St., New York City. Assistant Professor of Pathology. (4, 1934)
- Smith, Arthur H., M.S., Ph.D. Wayne University College of Medicine, Detroit 26, Mich. Professor of Physiological Chemistry. (1, 1923; 2, 1921; 5, 1933)
- Smith, Austin Edward, M.D., C.M., M.Sc.(Med.). American Medical Association, 535 N. Dearborn St., Chicago, Ill. Acting Secretary of the Council on Pharmacy and Chemistry, American Medical Association; Research Associate (Instructor) Dept. of Pharmacology, University of Chicago. (3, 1942)
- Smith, Clarence A., M.S., Ph.D. Standard Brands, Inc., 595 Madison Ave., New York City. Technical Director, Special Products Department. (1, 1921)
- Smith, David T. Duke Hospital, Durham, N. C. (5, 1943)
- Smith, Dietrich Conrad, A.M., Ph.D. University of Maryland School of Medicine, Lombard and Greene Sts., Baltimore. Associate Professor of Physiology. (1, 1937)
- Smith, Elinor Van Dorn, Ph.D. 5 Middle St., Hadley, Mass. Assistant Professor of Bacteriology, Smith College. (6, 1940)
- Smith, Elizabeth R. B., Ph.D. ½ Capt. Paul K. Smith, School of Aviation Medicine, Randolph Field, Texas. (2, 1938)
- Smith, Erma A., A.M., Ph.D., M.D. Iowa State College, Ames. Associate Professor of Physiology. (1, 1928)
- Smith, Fred M., M.D. State University of Iowa, Iowa City. Professor of the Theory and Practice of Medicine and Head of the Department. (1, 1925)
- Smith, George H., M.A., Ph.D., M.A.(hon.), Sc.D. School of Medicine, Yale University, New Haven, Conn. Professor of Immunology and Assistant Dean; Chairman, Department of Bacteriology, Yale University. (6, 1918)
- Smith, H. P., M.S., M.D. Columbia Univ., Coll. of Physicians and Surgeons, 630 West 168th St., New York 32, N. Y. Delafield Professor of Pathology. (1, 1937; 4, 1925)
- Smith, Homer W., M.S. (hon.), Sc.D. 477 First Ave., New York City. Professor of Physiology, New York University College of Medicine; Member, National Academy of Sciences. (1, 1923; 2, 1930)
- Smith, Lawrence Weld, M.D. 10 E. 75th St., New York 21, N. Y. (4, 1927)
- Smith, Lee Irvin, A.M., Ph.D. School of Chemistry, University of Minnesota, Minneapolis. Professor and Chief, Division of Organic Chemistry. (2, 1942)
- Smith, Margaret Cammack, A.M., Ph.D. University of Arizona, Tucson. Professor of Nutrition; Nutrition Chemist, Agricultural Experiment Station, School of Home Economics. (2, 1935; 5, 1933)
- Smith, Maurice I., M.D. National Institute of Health, Bethesda, Md. Principal Pharmacologist, U. S. Public Health Service. (1, 1920; 3, 1916)
- Smith, Paul K., Ph.D. AAF School of Aviation Medicine, Randolph Field, Texas. Chief, Laboratory of Pharmacology and Biochemistry; Major, Air Corps. (2, 1937; 3, 1937)
- Smith, Paul W., M.S., Ph.D. School of Medicine, University of Oklahoma, 801 E. 13th St., Oklahoma City. Assistant Professor of Pharmacology. (1, 1933)
- Smith, Philip Edward, M.S., Ph.D. 630 W. 168th St., New York City. Professor of Anatomy, Columbia University; Member of the National Academy of Sciences. (1, 1923)
- Smith, Ralph G., M.D., Ph.D. Tulane University, Station 20, New Orleans, La. Professor of Pharmacology. (3, 1929)
- Smith, R. Blackwell, Jr., S.M., Ph.D. Division of Pharmacology, Food and Drug Administration, Federal Security Agency, Washington, D. C. Pharmacologist and Assistant to the Chief. (3, 1944)
- Smith, Sedgwick E., Ph.D. U. S. Plant, Soil and Nutrition Lab., Ithaca, N. Y. Animal Physiologist and Geneticist. (5, 1945)
- Smith, Susan Gower, M.A. Duke University, Durham, N. C. Associate, Department of Medicine and Nutrition, School of Medicine. (5, 1939)
- Smith, Sybil L., A.M. Principal Experiment Station Administrator, Office of Experiment Stations, U.S.D.A., Washington, D. C. (5, 1940)
- Smith, Wilbur Kenneth, M.D. University of Rochester School of Medicine and Dentistry, 260 Crittenden Blvd., Rochester, N. Y. Associate Professor of Anatomy. (1, 1939)
- Smith, Willie W., M.A., Ph.D. 4710 Edgemoor Lane, Bethesda, Md. Associate Physiologist, National Institute of Health. (1, 1941)
- Smithburn, Kenneth C., M.D. Yellow Fever Research Institute, P. O. Box 49, Entebbe, Uganda, British East Africa. Staff Member, Interna-

- tional Health Division of The Rockefeller Foundation. (6, 1937)
- Smolens, Joseph, B.S. Wyeth Research Inst., 900 N. Broad St., Philadelphia, Pa. Fellow in Bacteriology. (6, 1943)
- Smythe, C. V., M.S., Ph.D. 5000 Richmond St., Philadelphia, Pa. Head of Biochemistry, Rohm & Haas Company. (2, 1934)
- Snell, Albert M., M.D. Mayo Clinic, Rochester, Minn. Head of Section on Medicine at Mayo Clinic; Professor in Medicine, Mayo Foundation Graduate School, University of Minnesota. (4, 1930)
- Snell, Esmond E., M.A., Ph.D. University of Wisconsin, Madison 6. Associate Professor of Biochemistry. (2, 1942)
- Snyder, Charles D., M.S., Ph.D. Baltimore 10, Md. Professor Emeritus of Experimental Physiology, Johns Hopkins Univ. (1, 1907)
- Snyder, Franklin Faust, M.D. Boston Lying-In Hospital, Boston, Mass. (1, 1936)
- Sobel, Albert E., Ch.E., M.A., Ph.D. Jewish Hospital of Brooklyn, Prospect Place and Classon Ave., Brooklyn, N. Y. Director of Chemical Laboratories; Lecturer in Biochemistry, Graduate Division, Brooklyn College; Lecturer in "Blood Chemistry", Hunter College. (2, 1939)
- Sobotka, Harry H., Ph.D. Mount Sinai Hospital, Fifth Ave. and 100th St., New York City. Head, Department of Chemistry. (2, 1932; 5, 1933)
- Solandt, Donald Young, M.A., M.D., Ph.D. University of Toronto, Toronto, Ont., Canada. Associate Professor of Physiology; Head of the Department of Physiological Hygiene. (1, 1937)
- Soley, Mayo H., M.D.\* University of California Medical School, The Medical Center, San Francisco. Associate Professor of Medicine and Assistant Dean. (1, 1943)
- Sollmann, Torald, M.D. Sc.D., LL.D. School of Medicine, Western Reserve University, 2109 Adelbert Rd., Cleveland, O. Dean and Professor of Pharmacology and Materia Medica, Emeritus. (1, 1902; 2, 1906; 3, 1908)
- Somogyi, Michael, Ph.D. 216 S. Kingshighway, St. Louis, Mo. Biochemist, Jewish Hospital of St. Louis. (2, 1927)
- Soskin, Samuel, M.D., M.A., Ph.D. Michael Reese Hospital, Chicago, Ill. Director of Metabolic and Endocrine Research; Professorial Lecturer in Physiology, University of Chicago. (1, 1930; 5, 1933)
- Soule, Malcolm H., Sc.D., LL.D. University of Michigan, Ann Arbor. Professor of Bacteriology, and Chairman of the Department of Bacteriology. (4, 1927; 6, 1925)
- Spain, Will C., M.D. 116 E. 53rd St., New York City. Clinical Professor of Medicine, Post-Graduate Medical School, Columbia University. (6, 1923)
- Speelman, C. R., M.A., Ph.D. National Naval Medical Center, Bethesda, Md. (1, 1940)
- Specht, Heinz, Ph.D. National Institute of Health, Rockville Pike, Bethesda, Md. Associate Research Physiologist. (1, 1941)
- Sperry, Roger W., Ph.D.\* Harvard University and Yerkes Laboratory of Primate Biology, Orange Park, Fla. Research Fellow in Biology. (1, 1945)
- Sperry, Warren M., M.S., Ph.D. 722 W. 168th St., New York City. Principal Research Biochemist, New York State Psychiatric Institute and Hospital; Assistant Professor of Biological Chemistry, College of Physicians and Surgeons, Columbia University. (2, 1929; 5, 1933)
- Spiegel, Ernest A., M.D. Temple University School of Medicine, Broad and Ontario Sts., Philadelphia, Pa. Professor of Experimental Neurology. (1, 1936)
- Spiegel-Adolf, Mona, M.D. Temple University School of Medicine, Broad St. at Ontario Ave., Philadelphia, Pa. Professor and Head of Department of Colloid Chemistry. (2, 1933)
- Spies, Tom D., M.D. Feb.-Nov. Hillman Hospital, Birmingham, Ala. Nov.-Feb. General Hospital, Cincinnati, O. Associate Professor of Medicine, Univ. of Cincinnati College of Medicine. Visiting Professor of Medical Research, Univ. of Alabama School of Medicine. Professor of Medical Research, Univ. of Texas School of Medicine. Director, Nutrition Clinic, Hillman Hospital, Birmingham, Ala. (3, 1941; 4, 1940; 5, 1938)
- Spink, Wesley W., M.D. University of Minnesota Hospital, Minneapolis. Associate Professor of Medicine, University of Minnesota Medical School. (3, 1940; 4, 1940; 6, 1940)
- Spohn, Adelaide, M.S., Ph.D. Elizabeth McCormick Memorial Fund, 848 N. Dearborn St., Chicago, Ill. (5, 1933)
- Spoor, Herbert J., Ph.D.\* 152nd St. and 89th Ave., Jamaica, N. Y. Mary Immaculate Hospital, Internship. (1, 1945)
- Sproul, Edith E., M.D. Columbia University, College of Physicians and Surgeons, New York City. Assistant Professor of Pathology. (4, 1941)
- Sprunt, Douglas H., M.D., M.S. Univ. of Tennessee, Memphis. Professor of Pathology. (4, 1934; 6, 1936)
- Stadie, William C., M.D. 821 Maloney Clinic, 36th and Spruce Sts., Philadelphia, Pa. Professor of Research Medicine, University of Pennsylvania. (2, 1922)
- Stainsby, Wendell J., M.D., C.M. Geisinger Memorial Hospital, Danville, Pa. Chief Physician. (6, 1930)

- Stanley, Wendell M., M.S., Ph.D., Sc.D. Rockefeller Institute for Medical Research, Princeton, N. J. Member; Member, National Academy of Sciences. (2, 1936)
- Stannard, James Newell, Ph.D. Research Division, Bureau of Medicine and Surgery, Navy Department, Washington 25, D. C. Lieutenant, H-V(5), USNR. (1, 1938)
- Stare, Frederick J., Ph.D., M.D. 25 Shattuck St., Boston 15, Mass. Associate Professor of Nutrition, Harvard Medical School and Harvard School of Public Health. (2, 1937; 5, 1942)
- Starr, Isaac, M.D. 817 Maloney Clinic, Hospital of the University of Pennsylvania, Philadelphia. Hartzell Research Professor of Therapeutics. (1, 1929; 3, 1942)
- Stavraky, George W., M.D., C.M., M.Sc. Medical School, University of Western Ontario, London, Ont., Canada. Associate Professor of Physiology. (1, 1937; 3, 1944)
- Stead, Eugene A., Jr., M.D.\* Emory University Medical School, Atlanta, Ga. Professor of Medicine. (1, 1945)
- Stearns, Genevieve, Ph.D. College of Medicine, State University of Iowa, Iowa City. Research Professor of Pediatrics. (2, 1932; 5, 1937)
- Steel, Matthew, Ph.D. Long Island College of Medicine, 350 Henry St., Brooklyn, N. Y. Professor of Biological Chemistry. (2, 1909)
- Steele, J. Murray, M.D. Welfare Hospital, Welfare Island, New York City. Associate Professor of Medicine, New York University; Director 3rd (New York University) Medical Division of Welfare Hospital. (1, 1936)
- Steenbock, Harry, M.S., Ph.D., Sc.D. University of Wisconsin, Madison. Professor of Biochemistry. (2, 1912; 5, 1933)
- Steggerda, F. R., M.A., Ph.D. 416 Natural History Building, University of Illinois, Urbana. Assistant Professor of Physiology. (1, 1934)
- Stehle, Raymond Louis, A.M., Ph.D. Faculty of Medicine, McGill University, Montreal, Canada. Professor of Pharmacology. (2, 1920; 3, 1922)
- Steigmann, Frederick, M.S., M.D. 348 S. Hamlin Ave., Chicago, Ill. Associate in Medicine, College of Medicine, University of Illinois; Associate Attending Physician, Cook County Hospital. (3, 1942)
- Steiman, S. E., M.A., Ph.D., M.D. 1874 Commonwealth Ave., Brighton, Mass. Assistant Physician, Metropolitan State Hospital, Waltham, Mass. (1, 1939)
- Steinbach, H. Burr, M.A., Ph.D. Washington University, St. Louis, Mo. Associate Professor of Zoology. (1, 1934)
- Steinberg, Bernhard, M.D. Toledo Hospital Institute of Medical Research, Toledo, O. Director of the Toledo Hospital Institute of Medical Research; Director of Clinical and Morbid Pathology; ideal Laboratories, The Toledo Hospital; Surgeon, U.S.P.H. (inactive). (4, 1928)
- Steiner, Paul E., M.D. The University of Chicago, Chicago, Ill. Associate Professor of Pathology. (4, 1939)
- Steinhardt, Jacinto, A.M., Ph.D. 1548 East-West Highway, Silver Spring, Md. Field Service Consultant, Office of Scientific Research and Development. (On loan to U. S. Navy.) (2, 1939)
- Steinhaus, Arthur H., M.S., Ph.D., M.P.E. 5315 Drexel Ave., Chicago, Ill. Professor of Physiology, George Williams College, Hyde Park. (1, 1928)
- Stekol, Jakob A., M.A., D.Sc. Amino Products Division, Rossford, O. Principal Research Chemist. (2, 1936)
- Stern, Kurt G., Ph.D. 85 Livingston St., Brooklyn, N. Y. Lecturer in Chemistry, Polytechnic Institute. (2, 1938)
- Stetten, DeWitt, Jr., M.D., Ph.D. 630 W. 168th St., New York City. Assistant Professor of Biochemistry, College of Physicians and Surgeons, Columbia University. (2, 1944)
- Stevens, S. Smith, Ph.D. Emerson Hall, Harvard University, Cambridge, Mass. Assistant Professor of Psychology. (1, 1937)
- Stewart, Fred W., M.D. Memorial Hospital, 444 E. 68th St., New York City. Pathologist; Associate Professor of Surgical Pathology, Cornell Medical School; Pathologist, New York State Department of Public Health, Division of Laboratories and Research. (4, 1928)
- Stewart, Harold L., M.D. The National Cancer Institute, Bethesda, Md. Senior Pathologist. (4, 1936)
- Stewart, Winifred Bayard, M.D., M.A. 2028 Delancey St., Philadelphia, Pa. Professor of Neurology, Woman's Medical College of Pennsylvania. (1, 1941)
- Stickney, J. Clifford, M.S., Ph.D.\* West Virginia University School of Medicine, Morgantown. Assistant Professor of Physiology. (1, 1944)
- Stiebeling, Hazel K., M.A., Ph.D. United States Department of Agriculture, Washington, D. C. Senior Food Economist, Bureau of Home Economics. (5, 1933)
- Stier, Theodore J. B., Ph.D. Indiana University Medical School, Bloomington. Associate Professor of Physiology. (1, 1938)
- Still, Eugene U., Ph.D. 9% Strong Cobb & Co., 2654 Lisbon Rd., Cleveland, O. (1, 1929)
- Stillman, Ernest G., M.D. 45 E. 75th St., New York City. (6, 1930)
- Stockton, Andrew Benton, M.D. Barracks Dispensary, U. S. Naval Supply Depot, Oakland, Calif. Assistant Clinical Professor of Medicine, Stanford Medical School; Commander, (M.C.) U.S.N.R. (3, 1931)

- Stokstad, E. L. Robert, Ph.D. Lederle Laboratories, Pearl River, N. Y. *Research Chemist.* (5, 1942)
- Stoland, O. O., M.S., Ph.D. 1845 Learnard Ave., Lawrence, Kan. *Professor of Physiology and Pharmacology, University of Kansas.* (1, 1913)
- Stone, William E., Ph.D.\* Department of Surgery, Wayne University College of Medicine, Detroit 26, Mich. *Research Associate with rank of Instructor.* (1, 1945)
- Stormont, Robert T., Ph.D. Naval Medical Research Institute, Bethesda, Md. *Lieutenant (j.g.) (M.C.) U.S.N.R.* (3, 1941)
- Stotz, Elmer H., Ph.D. New York State Agricultural Experiment Station, Cornell University, Geneva, N. Y. *Professor of Agricultural and Biological Chemistry, Cornell University.* (2, 1939)
- Stoughton, Roger W., M.S., Ph.D. Mallinckrodt Chemical Works, 3600 N. Second St., St. Louis, Mo. *Research Chemist.* (3, 1939)
- Strong, Frank M., M.A., Ph.D. Department of Biochemistry, University of Wisconsin, Madison. *Associate Professor of Biochemistry.* (2, 1941)
- Struck, Harold Carl, Ph.D. University of Illinois College of Medicine, 1853 W. Polk St., Chicago. *Assistant Professor of Pharmacology and Therapeutics.* (1, 1940)
- Stuart, Charles A., M.Sc., Ph.D. 372 Lloyd Ave., Providence, R. I. *Associate Professor of Biology, Brown University.* (6, 1935)
- Sturgis, Cyrus Cressey, M.D. Simpson Memorial Institute, Ann Arbor, Mich. *Director, Thomas Henry Simpson Memorial Institute for Medical Research; Chairman, Department of Medicine, University Hospital, and Professor of Medicine, University of Michigan.* (4, 1927)
- Subbarow, Y., Ph.D. Lederle Laboratories, Pearl River, N. Y. (2, 1939)
- Sugg, John Y., Ph.D. Cornell University Medical College, 1300 York Ave., New York City. *Assistant Professor of Bacteriology and Immunology.* (6, 1938)
- Sulkin, S. Edward, Ph.D. Southwestern Medical Foundation, Dallas, Texas. *Associate Professor of Bacteriology and Immunology.* (6, 1944)
- Sullivan, Michael Xavier, Ph.D. Chemo-Medical Research Institute, Georgetown University, 37th & O Sts., N. W., Washington, D. C. *Director and Research Professor of Chemistry.* (2, 1909)
- Sulzberger, Marion B., M.D. 962 Park Ave., New York City. *Lieutenant Commander, M.C., U.S.N.R., in charge of Dermatology and Syphilology, U. S. Naval Hospital, Brooklyn, N. Y.; Assistant Clinical Professor of Dermatology and Syphilology, Columbia University.* (6, 1936)
- Summerson, William H., M.A., Ph.D. Cornell University Medical College, 1300 York Ave., New York City. *Assistant Professor of Biochemistry.* (2, 1942)
- Sumner, James Batcheller, A.M., Ph.D. Dairy Building, Ithaca, N. Y. *Professor of Biochemistry, Cornell University Medical College.* (2, 1919)
- Sumwalt, Margaret, M.S., Ph.D. Medical School, University of Pennsylvania, Philadelphia. (1, 1934)
- Sunderman, F. William, M.D., Ph.D. University of Pennsylvania, Philadelphia. *Assistant Professor of Research Medicine.* (2, 1931)
- Sundstroem, Edward S., M.D. University of California, Berkeley. *Professor of Biochemistry.* (2, 1919)
- Sure, Barnett, M.S., Ph.D. University of Arkansas, Fayetteville. *Head of Department and Professor of Agricultural Chemistry.* (2, 1923; 5, 1933)
- Sutherland, George F., C.M., M.D., M.Sc. Crile General Hospital, Cleveland, O. Majar, M.C. (1, 1939)
- Sutton, T. Scott, M.Sc., Ph.D. Ohio State University, Columbus. *Assistant Professor; Associate, Ohio Agricultural Experiment Station, College of Agriculture.* (5, 1936)
- Svirbely, Joseph L., Ph.D. Industrial Hygiene Research Laboratory, National Institute of Health, Bethesda 14, Md. *Pharmacologist.* (3, 1945)
- Swain, Robert E., M.S., Ph.D., LL.D. 634 Mirada Ave., Stanford University, Calif. *Professor Emeritus of Chemistry.* (2, 1909)
- Swann, Howard G., M.S., Ph.D. Dept. of Pharmacology, University of Texas Medical School, Galveston. *Assistant Professor of Physiology. Captain, Aero Medical Laboratory, Wright Field, Dayton, O.* (1, 1940)
- Swanson, Pearl P., M.S., Ph.D. Iowa State College, Ames. *Professor of Foods and Nutrition, Dept. of Foods and Nutrition.* (5, 1933)
- Swanson, William W., M.S., M.D. 2376 E. 71st St., Chicago, Ill. *Assistant Professor of Pediatrics, Northwestern University.* (2, 1938)
- Sweeney, H. Morrow, M.S., Ph.D. School of Medical Sciences, University of South Dakota, Vermillion. *Professor of Physiology and Pharmacology and Head of the Department.* (1, 1939)
- Sweet, J. E., A.M., M.D., Sc.D. Unadilla, N. Y. *Emeritus Professor of Surgical Research, Cornell Medical College.* (1, 1913)
- Swift, Homer, M.D., D.Sc. 888 Park Ave., New York City. *Member, Rockefeller Institute for Medical Research; Physician to The Hospital of The Rockefeller Institute for Medical Research.* (6, 1920)
- Swift, Raymond W., M.S., Ph.D. Pennsylvania State College, State College. *Professor, Institute of Animal Nutrition.* (5, 1934)
- Swingle, Wilbur Willis, Ph.D. Princeton University, Princeton, N. J. *Professor of Biology.* (1, 1924)

- Tuft, Louis H., M.D. 1530 Locust St., Philadelphia, Pa. Assistant Professor of Medicine, Temple University Medical School; Chief of Clinic of Allergy and Applied Immunology, Temple University Hospital. (6, 1928)
- tum Suden, Caroline, M.A., Ph.D. 80 E. Concord St., Boston, Mass. Evans Research Fellow in Physiology, Boston University School of Medicine; Assistant, Evans Memorial Staff, Massachusetts Memorial Hospitals. (1, 1936)
- Tuohy, Edward B., M.S., M.D. Percy Jones General Hospital, Battle Creek, Mich. Assistant Professor of Anesthesiology, Mayo Foundation. Captain, M.C. (3, 1941)
- Turner, Abby H., Ph.D. Mount Holyoke College, South Hadley, Mass. Professor of Physiology. (1, 1928)
- Turner, William A., Ph.D. Bureau of Dairy Industry, U. S. Department of Agriculture, Beltsville, Md. Associate Chemist. (2, 1929)
- Tuttle, Waid Wright, M.A., Ph.D. State University of Iowa, Iowa City. Professor of Physiology. (1, 1925)
- Tweedy, Wilbur R., Ph.D. Loyola University School of Medicine, 706 S. Wolcott St., Chicago, Ill. Professor and Chairman, Department of Biological Chemistry. (2, 1931)
- Tyler, David B., Ph.D.\* California Institute of Technology, Pasadena. Hixon Fund Fellow. (1, 1943)
- Unna, Klaus R. W., M.D. 1853 W. Polk St., Chicago 12, Ill. Assistant Professor, Dept. of Pharmacology, Univ. of Illinois Coll. of Medicine. (1, 1941; 3, 1944; 5, 1942)
- Upton, Morgan, M.A., Ph.D. Dept. of Psychology, St. Lawrence University, Canton, N. Y. Assistant Director, British Ministry of Supply Mission, 404 A Bradford Building, 1800 K. St., N.W., Washington, D. C. (1, 1934)
- Urban, Frank, Ph.D., M.D. Research Hospital, University of Illinois, Chicago. Intern. (2, 1932)
- Vahlteich, Ella McCollum, M.A., Ph.D. 46 Hudson Ave., Edgewater, N. J. (5, 1933)
- Van Dyke, H. B., Ph.D., M.D. 630 W. 168th St., New York, N. Y. Professor of Pharmacology, Columbia University, College of Physicians and Surgeons. (1, 1925; 3, 1942)
- van Harreveld, Anthonie, M.A., M.D. California Institute of Technology, Pasadena. Associate Professor of Physiology. (1, 1941)
- Van Liere, Edward J., M.S., M.D., Ph.D. The School of Medicine, West Virginia University, Morgantown. Professor of Physiology and Dean. (1, 1927)
- Van Slyke, Donald D., Ph.D., Sc.D., M.D. Rockefeller Institute for Medical Research, 66th St. and York Ave., New York City. Member; Member, National Academy of Sciences. (2, 1905)
- van Wagenen, Gertrude, Ph.D. Yale University School of Medicine, New Haven, Conn. Associate Professor. (1, 1932)
- Van Winkle, Walton, Jr., M.D. Drug Division, Food and Drug Administration, Federal Security Agency, Washington, D. C. Senior Medical Officer. (3, 1939)
- Vars, Harry M., Ph.D. Harrison Department of Surgical Research, University of Pennsylvania Medical School, Philadelphia. Assistant Professor of Physiological Chemistry. (2, 1935; 5, 1935)
- Vennesland, Birgit, Ph.D. Dept. of Biochemistry, University of Chicago, Chicago, Ill. Assistant Professor. (2, 1944)
- Venning, Eleanor H., M.S., Ph.D. University Clinic, Royal Victoria Hospital, Pine Ave., Montreal, Quebec, Canada. Assistant Professor of Medicine, McGill Univ. (2, 1938)
- Vickery, Hubert B., M.S., Ph.D. Connecticut Agricultural Experiment Station, New Haven. Lecturer on the Chemistry of Proteins, Yale University; Biochemist in Charge, Connecticut Agricultural Experiment Station; Member, National Academy of Sciences. (2, 1923)
- Victor, Joseph, M.D. Research Service, First Division, Goldwater Memorial Hospital, Welfare Island, New York 17. Experimental Pathologist; Assistant Professor of Pathology, Columbia University College of Physicians and Surgeons. (4, 1935)
- Virtue, Robert W., Ph.D. 2134 E. Iliff Ave., Denver, Colo. Associate Professor of Chemistry, University of Denver. (2, 1939)
- Visscher, Maurice B., Ph.D., M.D. University of Minnesota, Minneapolis. Professor of Physiology. (1, 1927)
- Voegtlind, Carl, Ph.D. University of Rochester School of Medicine and Dentistry, Rochester, N. Y. Lecturer in Pharmacology. (1, 1908; 2, 1908; 3, 1908)
- von Haam, Emmerich, M.D. Ohio State University, Columbus. Professor of Pathology. (4, 1938)
- Von Oettingen, W. F., M.D., Ph.D. National Institute of Health, Division of Industrial Hygiene, Bethesda, Md. Principal Industrial Toxicologist. (3, 1925)
- Vorwald, Arthur J., Ph.D., M.D. Saranac Laboratory, Saranac Lake, N. Y. Pathologist. (4, 1937)
- Vos, Bert J., Ph.D., M.D. Division of Pharmacology, Food and Drug Administration, Washington, D. C. Associate Pharmacologist. (3, 1941)
- Waddell, J. A., M.D. Monroe Hill, Medical School, University of Virginia, Charlottesville. Professor of Pharmacology. (3, 1916)
- Waddell, James, Ph.D. E. I. duPont de Nemours & Co., New Brunswick, N. J. Director of the Biological Laboratory. (2, 1930; 5, 1935)

- Wadsworth, Augustus B., M.D. New York State Department of Health, Albany. Director, Division of Laboratories and Research. (4, 1935; 6, 1920)
- Waelsch, Heinrich, M.D., Ph.D. 722 West 168th St., New York 32, N. Y. Associate Research Biochemist, N. Y. State Psychiatric Institute and Hospital; Assistant Professor of Biological Chemistry, Columbia University. (2, 1941)
- Waisman, Harry A., M.S., Ph.D. Biochemistry Bldg., University of Wisconsin, Madison. Associate in Biochemistry. (2, 1944)
- Wakeman, Alfred J., Ph.D. Hatfield Hill Road, Bethany, Conn. Retired. (2, 1906)
- Wakerlin, George E., Ph.D., M.D. University of Illinois Medical School, 1853 W. Polk St., Chicago. Professor of Physiology. (1, 1933; 3, 1934)
- Wakim, Khalil G., M.D., Ph.D. University of Indiana Medical School, Bloomington. Professor of Physiology. (1, 1942)
- Wald, George, M.A., Ph.D. Biological Laboratories, Harvard University, Cambridge, Mass. (1, 1934)
- Walker, Arthur M., M.D. University of Pennsylvania, Philadelphia. Associate Professor of Pharmacology, Major, M.C. (1, 1932; 3, 1939)
- Walker, Burnham S., Ph.D., M.D. Boston University School of Medicine, 80 E. Concord St., Boston, Mass. Professor of Biochemistry. (2, 1940)
- Walker, Ernest Linwood, S.D. Second and Parnassus Aves., San Francisco, Calif. Professor of Tropical Med., The George Williams Hooper Foundation for Medical Research, University of California. (3, 1931)
- Wallace, George B., A.M., Sc.D. (hon.) M.D. 477 First Ave., New York City. Professor of Pharmacology, New York University College of Medicine. (1, 1901; 2, 1906; 3, 1909)
- Wallen-Lawrence, Zonja, Ph.D. 4534 W. Pine Blvd., St. Louis, Mo. Lecturer on Nutrition and Diet, Washington University School of Dentistry. (2, 1937)
- Walter, Carl W., M.D. Harvard Medical School, 25 Shattuck Street, Boston, Mass. Director, Laboratory for Surgical Research; Assistant Professor of Surgery, Harvard Medical School; Senior Associate in Surgery, Peter Bent Brigham Hospital. (4, 1942)
- Walters, Orville S., Ph.D., M.D. McPherson, Kan. Physician. (1, 1936)
- Walton, Robert P., M.A., Ph.D., M.D. Medical College of the State of South Carolina, Charleston. Professor of Pharmacology. (3, 1933)
- Walton, Seth T., V.M.D., M.S., Ph.D. City Health Department, Charlotte, N. C. Director of Laboratories and Research. (6, 1936)
- Walzer, Matthew, M.D. 20 Plaza St., Brooklyn, N. Y. Attending in Allergy, Jewish Hospital of Brooklyn. (6, 1924)
- Wang, Chi Che, M.S., Ph.D. 323 Belden Ave., Chicago, Ill. Research Chemist, Children's Memorial Hospital; Assistant Professor, Dept. of Physiology, Northwestern University Medical College, Chicago. (2, 1922; 5, 1933)
- Wang, Shih-Chun, M.D.\* Columbia University College of Physicians and Surgeons, 630 W. 168th St., New York City. Assistant Professor in the Department of Physiology. (1, 1943)
- Wangensteen, Owen Harding, M.D. University of Minnesota, Minneapolis. Professor of Surgery. (4, 1931)
- Warner, Emory D., M.D. Medical Laboratories Bldg., Iowa City, Ia. Professor of Pathology. (4, 1937)
- Warren, Charles O., Ph.D., M.D. Cornell University Medical College, 1300 York Ave., New York City. Assistant Professor of Physiology and Anatomy. (1, 1941)
- Warren, Madeleine Field, A.M., Ph.D. 9 High Rock St., Needham, Mass. Harvard School of Public Health, 55 Shattuck St., Boston, Mass. Associate in Physiology. (1, 1933)
- Warren, Shields, M.D. Palmer Memorial Hospital, 195 Pilgrim Rd., Boston, Mass. Pathologist, New England Deaconess Hospital; Assistant Professor of Pathology, Harvard Medical School. (4, 1929)
- Wartman, William Beckman, M.D. Western Reserve University, 2035 Adelbert Rd., Cleveland, O. Assistant Professor of Pathology. (4, 1940)
- Wasteneys, Hardolph, Ph.D., F.R.S.C. University of Toronto, Toronto, Canada. Professor and Head of Department of Biochemistry. (2, 1915)
- Wastl, Helene, M.D. Hahnemann Medical College and Hospital, Philadelphia, Pa. Research Associate in Pharmacology and Anatomy. (1, 1939)
- Waterman, Robert E., B.S. Schering Corporation, 86 Orange St., Bloomfield, N. J. Vice-President. (2, 1940)
- Waters, Ralph Milton, M.D. 1300 University Ave., Madison, Wis. Professor of Anesthesia, University of Wisconsin. (3, 1937)
- Watson, Cecil J., M.D., Ph.D. Department of Medicine, University Hospital, Minneapolis, Minn. Professor and Head of Department of Medicine. (4, 1941)
- Watson, John B., A.M., Ph.D., LL.D. 420 Lexington Ave., New York City. Vice President of the J. Walter Thompson Co. (1, 1907)
- Waud, Russell A., M.D., M.Sc., Ph.D. M School, University of Western Ontario,

- Canada. Professor of Pharmacology. (1, 1925; 3, 1931)
- Waugh, David F., Ph.D.\* Department of Biology and Biological Engineering, Massachusetts Institute of Technology, Cambridge. Assistant Professor of Physical Biology. (1, 1943)
- Wearn, Joseph T., M.D. Lakeside Hospital, Cleveland, O. Professor of Medicine, Western Reserve University; Director of Medicine, Lakeside Hospital. (1, 1921)
- Weatherby, J. H., M.A., Ph.D. Naval Air Station Dispensary, Pensacola, Fla. Research Associate in Pharmacology, Medical College of Virginia; Lieutenant (M.C.) U.S.N.R. (3, 1941)
- Weber, Clarence J., M.D., Ph.D. University of Kansas Hospitals, Kansas City. Assistant Professor of Research Medicine. (2, 1931)
- Webster, Bruce, M.D., C.M. Cornell University Medical College, 1300 York Ave., New York City. Assistant Professor Medicine; Associate Attending Physician, New York Hospital. (5, 1935)
- Weed, Lewis H., A.M., M.D., Sc.D. Johns Hopkins University Medical School, Baltimore, Md. Professor of Anatomy. (1, 1919)
- Wégrin, René, M.D. Department of Medicine, Presbyterian Hospital, 622 W. 168th St., New York City. (1, 1941)
- Weichert, Charles K., Ph.D. University of Cincinnati, Cincinnati, O. Professor of Zoology. (1, 1935)
- Weil, Alfred J., M.D. Lederle Laboratories, Inc., Pearl River, N. Y. Immunologist. (6, 1940)
- Weil, Arthur, M.D. 161 East 71st St., New York, N. Y. (4, 1940)
- Weil, Leopold, Ph.D. Eastern Regional Research Laboratory, U. S. Department of Agriculture, Chestnut Hill Station, Philadelphia, Pa. Chemist. (2, 1942)
- Weir, Everett G., M.S., Ph.D. School of Medicine, Howard University, Washington, D. C. Assistant Professor of Physiology. (1, 1941)
- Weiss, Charles, M.S., Ph.D., M.D. Jewish Hospital, York & Tabor Roads, Philadelphia, Pa. Director of Laboratories. (4, 1934; 6, 1920)
- Weiss, Emil, M.D., Ph.D. P. O. Box 714, Chicago, Ill. Pathologist, Chicago Eye, Ear, Nose and Throat Hospital. (6, 1927)
- Weiss, Paul, Ph.D. University of Chicago, Chicago, Ill. Professor of Zoology. (1, 1936)
- Welch, Arnold D., Ph.D., M.D. Western Reserve University School of Medicine, Cleveland, O. Professor of Pharmacology. (3, 1942; 5, 1944)
- Welch, Henry, Ph.D. Bacteriological Section, U. S. Food and Drug Administration, Washington, D. C. Senior Bacteriologist. (6, 1932)
- Weld, Charles Beecher, M.A., M.D. Dalhousie University, Halifax, N.S., Canada. Professor of Physiology. (1, 1936)
- Weld, Mrs. Julia T. College of Physicians and Surgeons, 630 W. 168th St., New York City. Research Associate in Pathology. (6, 1920)
- Welker, William H., A.C., Ph.D., D. Sc. 1853 W. Polk St., Chicago, Ill. Professor of Biological Chemistry and Head of the Department, College of Medicine, University of Illinois. (2, 1906)
- Weller, Carl Vernon, M.D. 1130 Fair Oaks Parkway, Ann Arbor, Mich. Professor of Pathology and Chairman, Department of Pathology, University of Michigan. (4, 1923)
- Wells, Herbert S., M.D. 318 Millard Hall, University of Minnesota, Minneapolis 14. Professor of Biophysics (temp.) and Baruch Fellow in Physical Medicine. (1, 1932)
- Wells, Joseph Albert, M.S., Ph.D. Northwestern University Medical School, Chicago, Ill. Associate in Pharmacology. (3, 1944)
- Welsh, John H., Ph.D.\* Biological Laboratories, Harvard University, 16 Divinity Ave., Cambridge 38, Mass. Associate Professor of Zoology. (1, 1945)
- Wendel, William B., Ph.D. Department of Biochemistry, Tulane University, 6501 St. Charles Ave., New Orleans 15, La. Professor of Biochemistry. (2, 1932)
- Werkman, C. H., Ph.D. Science Hall, Iowa State College, Ames. Professor in Charge, Department of Bacteriology. (2, 1942)
- Werle, Jacob M., M.D.\* 4478 Broadale Ave., Cleveland, O. 1st Lieutenant, M. C. (1, 1943)
- Werner, Harold W., Ph.D. The Wm. S. Merrell Co., Lockland Station, Cincinnati, O. Director of Pharmacology Research. (3, 1942)
- Wertenberger, Grace E., S.M., Ph.D.\* Women's Medical College of Pennsylvania, Philadelphia. Assistant Professor of Physiology. (1, 1943)
- Wesson, Laurence Goddard, Ph.D. Forsyth Dental Infirmary, Boston, Mass. Research Biochemist. (2, 1929; 3, 1932)
- West, Edward S., M.S., Ph.D. University of Oregon Medical School, Portland. Professor of Biochemistry. (2, 1925)
- West, Randolph, M.A., M.D. 622 W. 168th St., New York City. Associate Professor of Medicine, Columbia University. (2, 1931)
- Westerfeld, Wilfred Wiedey, Ph.D. Syracuse University College of Medicine, Syracuse 10, N. Y. (2, 1944)
- Weymouth, Frank W., Ph.D. Stanford University, Calif. Professor of Physiology and Executive of the Department. (1, 1917)
- Wheeler, George W., M.D. New York Hospital, 525 E. 68th St., New York City. Superintendent. (6, 1920)
- Wheeler, Kenneth M., Ph.D. Bureau of Laboratories, Connecticut State Department of Health, 1179 Main St., Hartford. Research Microbiologist. (6, 1938)

- Wheeler, Mary W., M.A. Division of Laboratories and Research, New York State Department of Health, Albany. *Associate Bacteriologist.* (6, 1933)
- Wheeler, Ruth, Ph.D. Vassar College, Poughkeepsie, N. Y. *Professor Emeritus of Physiology and Nutrition.* (2, 1915; 5, 1933)
- Wheelon, Homer, M.S., M.D. American Bank Bldg., Seattle, Wash. (1, 1919)
- Whipple, George H., M.D., Sc.D. University of Rochester, Rochester, N. Y. *Professor of Pathology and Dean of the School of Medicine and Dentistry; Member of the National Academy of Sciences.* (1, 1911; 4, 1913)
- White, Abraham, M.A., Ph.D. 333 Cedar St., New Haven, Conn. *Associate Professor of Physiological Chemistry, Medical School, Yale University.* (2, 1934; 5, 1937)
- White, Frank D., Ph.D., F.I.C. Medical College, University of Manitoba, Winnipeg, Canada. *Assistant Professor of Biochemistry, Faculty of Medicine.* (2, 1931)
- White, Harvey Lester, M.D. Station Hospital, A.P.O. 726, Seattle, Wash. *Colonel, M.C.; Associate Professor of Physiology, Washington University Medical School, St. Louis, Mo.* (1, 1923)
- White, Julius, A.M., Ph.D. National Cancer Institute, Bethesda, Md. *Senior Biochemist. (At present on leave of absence while in Army of U.S.)* (2, 1937)
- White, Paul Dudley, M.D., Massachusetts General Hospital, Boston. *Lecturer in Medicine, Harvard Medical School; Physician (in charge of Cardiac Clinics and Laboratory), Mass. General Hospital.* (3, 1921)
- Whitehead, Richard W., M.A., M.D. University of Colorado School of Medicine, 4200 E. Ninth Ave., Denver. *Professor of Physiology and Pharmacology.* (1, 1933; 3, 1928)
- Wiener, Alexander S., M.D. 64 Rutland Rd., Brooklyn, N. Y. *Bacteriologist and Serologist to Office of Chief Medical Examiner of New York City; Head of Transfusion Division, Jewish Hospital of Brooklyn.* (6, 1932)
- Wiersma, Cornelis A. G., M.A., Ph.D. California Institute of Technology, Pasadena. *Associate Professor of Physiology.* (1, 1941)
- Wiggers, Carl J., M.D., Sc.D. Medical School, Western Reserve University, Cleveland, O. *Professor and Director of Physiology.* (1, 1907; 3, 1909)
- Wiggers, Harold C., Ph.D. College of Medicine, University of Illinois, 1853 W. Polk St., Chicago. *Associate Professor of Physiology.* (1, 1935)
- Wigodsky, Herman S., Ph.D., M.D.\* AAF School Aviation Medicine, Randolph Field, Texas. *Chief, Dept. of Physiology.* (1, 1943)
- Wikler, Abraham, M.D. U. S. Public Health Service Hospital, Lexington, Ky. *Surgeon (R), U. S. Public Health Service.* (3, 1944)
- Wilde, Walter S., Ph.D.\* Carnegie Institution of Washington, Department of Embryology, Wolfe and Madison Sts., Baltimore 5, Md. *Junior Investigator, Assistant Professor of Physiology.* (1, 1944)
- Wilder, Russell M., Ph.D., M.D. Mayo Clinic, Rochester, Minn. *Professor of Medicine, Mayo Foundation, University of Minnesota.* (1, 1921; 4, 1924; 5, 1933)
- Wiley, Frank H., M.S., Ph.D. Food and Drug Administration, Federal Security Agency, Washington 25, D. C. *Chemist.* (2, 1933)
- Wilhelme, Jane Russell, Ph.D. Yale University School of Medicine, 333 Cedar St., New Haven, Conn. *Instructor in Physiological Chemistry.* (1, 1939)
- Wilhelmi, Alfred E., Ph.D. 333 Cedar St., New Haven, Conn. Yale University School of Medicine. *Assistant Professor of Physiological Chemistry.* (2, 1942)
- Wilhelmi, Charles Martel, M.D. Creighton University School of Medicine, Omaha, Neb. *Professor of Physiology.* (1, 1931)
- Wilkerson, Vernon A., M.D., Ph.D. Howard University Medical School, Washington, D. C. *Professor and Head of Department of Biochemistry.* (2, 1936)
- Williams, Edwin G., M.D., D.T.M., D.T.H. National Institute of Health, Bethesda 14, Md. *Senior Surgeon U. S. Public Health Service, Director of Research, U. S. P. H. S. Hospital, Lexington, Ky.* (3, 1944)
- Williams, Harold H., Ph.D. Department of Biochemistry, Cornell University, Ithaca, N. Y. (2, 1938; 5, 1936)
- Williams, Horatio B., M.D., Sc.D. Box 893, Greenwich, Conn. *Dalton Professor of Physiology Emeritus, Columbia University.* (1, 1912)
- Williams, J. W., M.S., Ph.D. University of Wisconsin, Chemistry Bldg., Madison. *Professor of Chemistry.* (2, 1944)
- Williams, Ray D., M.S., M.D. 6334 Waterman St., St. Louis, Mo. *Assistant Professor of Clinical Medicine, Washington University.* (5, 1941)
- Williams, Robert Hardin, M.D. Thorndike Laboratory, Boston City Hospital, Boston, Mass. *Associate in Medicine, Harvard Medical School; Assistant Physician, Thorndike Memorial Laboratory; Junior Visiting Physician, II and IV Medical Services (Harvard) Boston City Hospital.* (4, 1940)
- Williams, Robert R., M.S., D.Sc. 297 Summit Ave., Summit, N. J. *Chemical Consultant, Bell Telephone Laboratories.* (2, 1919; 5, 1941)

- Williams, Roger J., Ph.D., D.Sc. University of Texas, Department of Chemistry, Austin. *Professor of Chemistry; Director, Biochemical Institute.* (2, 1931; 5, 1945)
- Wills, J. H., M.S., Ph.D.\* University of Rochester, School of Medicine and Dentistry, Rochester, N. Y. *Associate in Pharmacology.* (1, 1943)
- Wilson, David Wright, M.S., Ph.D. University of Pennsylvania Medical School, Philadelphia. *Benjamin Rush Professor of Physiological Chemistry.* (1, 1915; 2, 1915)
- Wilson, Frank N., M.D. University Hospital, Ann Arbor, Mich. *Professor of Medicine, University of Michigan.* (4, 1925)
- Wilson, Karl M., M.D. University of Rochester, School of Medicine, Rochester, N. Y. *Professor of Obstetrics and Gynecology.* (4, 1927)
- Wilson, P. W., Ph.D. Department of Agricultural Bacteriology, University of Wisconsin, Madison. *Associate Professor in Agricultural Bacteriology.* (2, 1939)
- Wilson, Robert H., Ph.D. U. S. Dept. of Agriculture, Western Regional Research Laboratory, 800 Buchanan St., Albany, Calif. *Pharmacologist.* (3, 1937)
- Winder, Claude V., Sc.D. 1927 Dexter Ave., Ann Arbor, Mich. *Pharmacologist, Parke, Davis & Company, Detroit, Mich.* (1, 1938)
- Windle, William Frederick, Ph.D. Northwestern University Medical School, 303 E. Chicago Ave., Chicago, Ill. *Professor of Neurology and Director of the Institute of Neurology.* (1, 1937)
- Winkenwerder, Walter LaF., M.D. Brooklandville, Md. *Associate in Medicine, Johns Hopkins Medical School.* (6, 1938)
- Winkler, Alexander Woodward, A.M., M.D. New Haven Hospital, 789 Howard Ave., New Haven, Conn. *Assistant Professor of Medicine, Yale University School of Medicine.* (1, 1940)
- Winter, Charles A., Ph.D. University of Oklahoma, School of Medicine, 801 E. 13th St., Oklahoma City. *Associate Professor of Physiology.* (1, 1940)
- Winter, Irwin Clinton, Ph.D., M.D. University of Oklahoma School of Medicine, Oklahoma City. *Associate Professor in Pharmacology; Captain, M.C.* (3, 1941)
- Winters, Jet C., M.A., Ph.D. University of Texas, Austin. *Professor of Home Economics.* (5, 1933)
- Winternitz, M. C., M.D. Yale University School of Medicine, New Haven, Conn. *Anthony N. Brady Professor of Pathology.* (4, 1913)
- Wintersteiner, Oskar, Ph.D. The Squibb Institute for Medical Research, New Brunswick, N. J. *Head, Division of Organic Chemistry; Honorary Professor of Biochemistry, Rutgers University.* (2, 1930)
- Wintrobe, Maxwell Myer, M.D., Ph.D. University of Utah School of Medicine, Salt Lake City. *Professor and Head of the Department of Internal Medicine.* (4, 1940)
- Wiseman, Bruce Kenneth, M.D. Kinsman Hall, Ohio State University, Columbus. *Professor and Chairman of Department of Medicine; Assistant Director of Medical Research.* (4, 1932)
- Wislocki, George B., M.D. Harvard University Medical School, 25 Shattuck St., Boston, Mass. *Parkman Professor of Anatomy.* (1, 1924)
- Witebsky, Ernest, M.D. Buffalo General Hospital, 100 High St., Buffalo, N. Y. *Professor of Bacteriology and Immunology.* (6, 1935)
- Wittich, Frederick W., M.A., M.D. 401 La Salle Medical Bldg., Minneapolis, Minn. *City Physician, General Hospital, Member Glen Lake Sanitarium Staff.* (6, 1944)
- Witzemann, Edgar J., M.A., Ph.D. Service Memorial Building, University of Wisconsin, Madison. *Associate Professor of Physiological Chemistry.* (2, 1925)
- Wolbach, S. Burt, M.D. Harvard University Medical School, 25 Shattuck St., Boston, Mass. *Shattuck Professor of Pathological Anatomy; Member, National Academy of Sciences.* (4, prior to 1920)
- Wolff, Harold G., M.D., M.A. New York Hospital, 525 E. 68th St., New York City. *Associate Professor of Medicine, Cornell University Medical College; Associate Attending Physician, New York Hospital.* (1, 1930; 3, 1942)
- Wood, Earl H., M.S., Ph.D., M.D.\* Mayo Aeromedical Unit, Mayo Foundation, Rochester, Minn. *Assistant in Physiology.* (1, 1943)
- Wood, Harland G., Ph.D. Dept. of Physiology, University of Minnesota, Minneapolis. *Associate Professor, Physiological Chemistry.* (2, 1944)
- Wood, Horatio C., Jr., M.D., Ph.M. 319 S. 41st St., Philadelphia, Pa. *Professor of Pharmacology and Therapeutics, University of Pennsylvania; Professor of Materia Medica, Philadelphia College of Pharmacy and Science.* (3, 1908)
- Woodbury, Robert A., Ph.D., M.D. University of Georgia, School of Medicine, Augusta. *Professor of Pharmacology.* (1, 1936; 3, 1941)
- Woodruff, Lorande Loss, A.M., Ph.D. Yale University, New Haven, Conn. *Professor of Protozoology; Member, National Academy of Sciences.* (1, 1910)
- Woods, Alan C., M.D. Wilmer Institute, Johns Hopkins Hospital, Baltimore, Md. *Ophthalmologist-in-Chief; Acting Professor of Ophthalmology, Johns Hopkins University; Director, Wilmer Ophthalmological Institute.* (6, 1918)

## ALPHABETICAL LIST OF ALL MEMBERS OF THE SIX SOCIETIES

- Woods, Ella, A.M., Ph.D. University of Idaho, Moscow. Home Economist, Experiment Station. (2, 1925; 5, 1933)
- Woodward, Alvalyn E., M.S., Ph.D. University of Michigan, Ann Arbor. Assistant Professor of Zoology. (1, 1932)
- Woodyatt, Rollin T., M.D. 237 E. Delaware Place, Chicago, Ill. Professor of Medicine, Rush Medical College, University of Chicago. (2, 1912)
- Woolley, Dillworth W., Ph.D. Rockefeller Institute for Medical Research, 66th St., and York Ave., New York City. Fellow. (5, 1941)
- Woolsey, Clinton N., M.D. Johns Hopkins University School of Medicine, Baltimore, Md. Associate in Physiology. (1, 1938)
- Wright, Angus, M.D. University of Southern California Medical School, 657 S. Westlake Ave., Los Angeles. Pathologist, California Hospital. (4, 1935)
- Wright, Arthur W., M.D. Albany Medical College, New Scotland Ave., Albany, N. Y. Professor of Pathology and Bacteriology. (4, 1941)
- Wright, Charles Ingham, M.S., Ph.D. National Institute of Health, Bethesda, Md. Senior Pharmacologist, U. S. Public Health Service. (1, 1935; 3, 1936)
- Wright, George G., Ph.D. Dept. of Chemistry, California Institute of Technology, Pasadena. National Research Fellow. (6, 1943)
- Wright, Harold N., M.S., Ph.D. University of Minnesota, Minneapolis. Associate Professor of Pharmacology. (3, 1933)
- Wright, Sydney L., M.A., Ph.D. Endsmeat Farm, Glenside, Pa. (2, 1933)
- Wulzen, Rosalind, M.S., Ph.D. Oregon State College, Corvallis. Assistant Professor of Zoology. (1, 1916)
- Wyckoff, Ralph W. G., Ph.D. U. S. Public Health Service, National Institute of Health, Bethesda, Md. Senior Scientist. (6, 1940)
- Wyman, Jeffries, Jr., Ph.D. Biological Laboratories, Harvard University, Cambridge, Mass. Associate Professor of Zoology. (1, 1928)
- Wyman, Leland C., Ph.D. Boston University School of Medicine, Boston, Mass. Associate Professor of Physiology. (1, 1927)
- Wynne, Arthur M., M.A., Ph.D., F.R.S.C. Department of Biochemistry, University of Toronto, Toronto, Canada. Professor of Biochemistry. (2, 1940)
- Yerkes, Robert M., Ph.D. Yale Laboratories of Primate Biology, 333 Cedar St., New Haven, Conn. Professor of Psychobiology, Yale University; Member of the National Academy of Sciences. (1, 1904)
- Yonkman, Frederick F., Ph.D., M.D. Ciba Pharmaceutical Products, Inc., Summit, N. J. Chief Pharmacologist. (3, 1931)
- Youmans, William Barton, M.A., Ph.D., M.D. University of Oregon Medical School, Portland. Professor of Physiology. (1, 1939)
- Young, A. G., Ph.D., M.D. 520 Commonwealth Ave., Boston, Mass. Assistant Professor of Therapeutics, Boston University School of Medicine; Medical Director, Cory Hill Hospital, Brookline. (3, 1925)
- Young, E. G., Ph.D., F.R.S.C. Dalhousie University, Halifax, N. S., Canada. Professor of Biochemistry. (2, 1925)
- Youngburg, Guy E., M.S., Ph.D. 66 Park Circle, Eggertsville, Buffalo, N. Y. Professor of Biological Chemistry, University of Buffalo. (2, 1927)
- Yuile, Charles L., M.D., C.M. University of Rochester School of Medicine and Dentistry, 260 Crittenden Blvd., Rochester, N. Y. Associate Professor of Pathology. (4, 1941)
- Zechmeister, L. California Institute of Technology, Pasadena. Professor of Organic Chemistry. (2, 1941)
- Zeckwer, Isolde T., M.D. School of Medicine, University of Pennsylvania, Philadelphia. Assistant Professor of Pathology. (1, 1934; 4, 1927)
- Zeldis, Louis Jenrette, M.D. Emory University School of Medicine, Atlanta, Ga. Assistant Professor of Pathology. (4, 1945)
- Zimmerman, Harry M., M.D., Lt. Comdr. (M.C.) USNR 489 Central Ave., New Haven, Conn. (4, 1933)
- Zweifach, Benjamin W., Ph.D.\* Department of Biology, New York University, Washington Square, New York 3, N. Y. Research Associate. (1, 1945)
- Zwemer, Raymond L., Ph.D. 5003 Battery Lane, Bethesda 14, Md. College of Physicians and Surgeons, Columbia University, 630 W. 168th St., New York City. Assistant Professor of Anatomy. On leave: Depl. of State, Washington, D. C. (1, 1930)

## SUMMARY OF MEMBERSHIP

The American Physiological Society.....	905
The American Society of Biological Chemists.....	638
The American Society for Pharmacology and Experimental Therapeutics.....	321
The American Society for Experimental Pathology.....	306
The American Institute of Nutrition.....	293
American Association of Immunologists.....	265
Total Members by Societies.....	2728

- Spaeth, Reynold A. (1) January 26, 1925.  
Spencer, Henry James (5) 1944.  
Sternberg, G. M. (1) November 3, 1915.  
Stevens, Herman C. (1) May 27, 1934.  
Stewart, Colin C. (1) January 22, 1944.  
Stewart, G. N. (1, 3, 4) May 28, 1931.  
Stiles, Percy G. (1) July 5, 1936.  
Storey, Thomas A. (1) October 27, 1943.  
Straus, Henry W. (6) 1937.  
Tait, John (1) October 21, 1944.  
Terry, Oliver P. (1) December 6, 1933.  
Thatcher, Roscoe Wilfred (2) December 6, 1933.  
Thompson, Wm. G. (1) October 27, 1927.  
Trask, James D. (6) May 24, 1942.  
Underhill, Frank P. (1, 2, 3) June 28, 1932.  
Van Slyke, Lucius L. (2) September 30, 1931.  
Vaughan, Victor C. (1, 4) October 21, 1929.  
Vincent, S. (1) December 31, 1933.
- Von Brücke, Ernest T. (1) June 12, 1941.  
von Voit, C. (1h) January 31, 1908.  
Wallace, Edward W. (3) July 11, 1943.  
Walton, D. C. (3) March 6, 1942.  
Warren, Joseph W. (1) December 20, 1916.  
Warthin, Aldred Scott (4) May 23, 1931.  
Webster, Leslie T. (4) July 12, 1943.  
Webster, Ralph W. (2) July 2, 1930.  
Weil, Richard (3, 6) November 19, 1917.  
Weiss, Soma (3) January 31, 1942.  
Welch, William H. (1, 4h) April 30, 1934.  
Wells, H. Gideon (2, 4, 6) April 26, 1943.  
Westbrook, Frank F. (1) October 21, 1918.  
Wherry, William Buchanan (4) November 1, 1936.  
Wiley, Harvey W. (2) June 30, 1930.  
Woelfel, A. (1) January 31, 1920.  
Wood, Horatio C. (1) January 3, 1920.  
Zinsser, Hans (4, 6) September 4, 1940.

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- STUART, H. C. Findings on examinations of newborn infants and infants during the neonatal period which appear to have a relationship to the diets of their mothers during pregnancy, 271.  
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- SWANSON, M. A. See CORI, SWANSON AND CORI, 234.
- WILKINS, W. AND W. H. SEBRELL. Developments in public health nutrition appraisal, 253.